Preventing Cervical Cancer with HPV Testing

What can we learn for the Swiss health system from evidence collected for the health systems of other countries?

A systematic review of current health economic evaluations

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Dr. Martina Hahn
aus Deutschland

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Projektbegleitung:

PD Dr. phil. Matthias Schwenkglenks
Head of Research, Institute of Pharmaceutical Medicine (ECPM),
University of Basel
Head, Medical Economics Unit, Epidemiology,
Biostatistics and Prevention Institute (EBPI),
University of Zurich

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2 Nomenclature, Glossary, Abbreviations

2.1 Nomenclature of cytological and histological findings

The following table provides an overview of the nomenclature of cytological and histological findings and their abbreviations [1].

Table 1: Nomenclature of cytological and histological findings

Bethesda System for the classification of cytological findings		WHO nomenclature for histological analyses	
NILM	Negative for intraepithelial lesions and malignancies		
ASC-US	Atypical squamous cells of undetermined significance		
ASC-H	Atypical squamous cells – cannot exclude HSIL		
LSIL	Low-grade Squamous Intraepithelial Lesion	CIN1	Cervical intraepithelial neoplasia mild dysplasia
HSIL	High-grade Squamous Intraepithelial Lesion	CIN2	Cervical intraepithelial neoplasia Moderate dysplasia
		CIN3	Cervical intraepithelial neoplasia Severe dysplasia / carcinoma in situ

In this thesis, the term “cytology negative” is often used instead of NILM.

2.2 Glossary, Abbreviations

Table 2: Glossary, Abbreviations

Acronym	Explanation
AIS	Adenocarcinoma in situ
ARTISTIC	UK Randomized Controlled Trial [2-4]
ATHENA	US “Addressing the Need for Advanced HPV Diagnostics” Study evaluating the clinical performance of cobas HPV assay with partial genotyping and different triage strategies for HPV-positive women [5]
BAG	Swiss Federal Office of Public Health (“Bundesamt für Gesundheit”)
C	Comparator
CCCaST	Canadian Cross Sectional Study [6]
CHF	Swiss Francs
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CIR	Cumulative Incidence Rate
CIS	Carcinoma in Situ
Conization	A treatment of precancerous lesions by removal of the affected area from the cervix. Different techniques of conization are available; one of these is LEEP (see below).

Cyt	cytological testing
EURONHEED	European Network of Health Economic Evaluation Databases
FPHT	“Finnish Public Health Trial” [7-10]
GDP	Gross Domestic Product
HPV	Human Papilloma Virus
hrHPV	High risk Human Papilloma Viruses
I	Intervention
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention to Treat
KPNC	Kaiser Permanente Cohort Study [11]
LBC	Liquid based cytology
LEEP	Loop Electrosurgical Excision Procedure, a treatment of precancerous lesions by removal of the affected area from the cervix
LYG	Life Years Gained
M	Month
MeSH	Medical Subjects Headings
n.a.	Not applicable
Neg	Negative
neg cyt/ cyt neg	Tested negative with a cytological test
neg HPV/ HPV neg	Tested negative with an HPV test
NPV	Negative predictive value
NTCC	Italian “New Technologies for **Cervical** Cancer (**NTCC**) screening study” [12-15]
OECD	Organization for Economic Co-operation and Development
POBASCAM	Dutch population-based randomized controlled trial for the implementation of high-risk HPV testing in cervical screening according to [16, 17]
Pap	Papanicolaou test
pos cyt/ cyt pos	Tested positive with a cytological test
pos HPV/ HPV pos	Tested positive with an HPV test
PPP	Purchasing Power Parity
PPV	Positive predictive value
RCT	Randomized Controlled Trial
RR	Rate Ratio
Swedescreen	Swedish Randomized Controlled Trial [18, 19]
y	Year(s)

3 Abstract

In Switzerland 90 women die of cervical cancer every year and 240 fall ill with the disease. In the last 30 years both the incidence and mortality of cervical cancer have steadily declined. This is attributed mainly to screening with the Pap test, named after its inventor George Papanicolaou. However this test is now challenged for its low sensitivity and more and more countries are changing their cervical cancer screening strategies to Human Papilloma Virus (HPV) tests or are considering so.
This thesis aims to make a recommendation for the future of cervical cancer screening in Switzerland based on a systematic review of the clinical and health economic evidence of other industrialized countries, and a transferability analysis of its results to the Swiss setting. The focus of this thesis is on unvaccinated women.
The following research questions were pursued:

- What is the best screening strategy with the highest clinical effectiveness to prevent cervical cancer at the lowest burden of follow up?
- How does the optimal algorithm for screening with the HPV test compare to screening with the Pap test in terms of incremental cost effectiveness?
- Are relevant barriers for the implementation of HPV based screening in Switzerland identified?

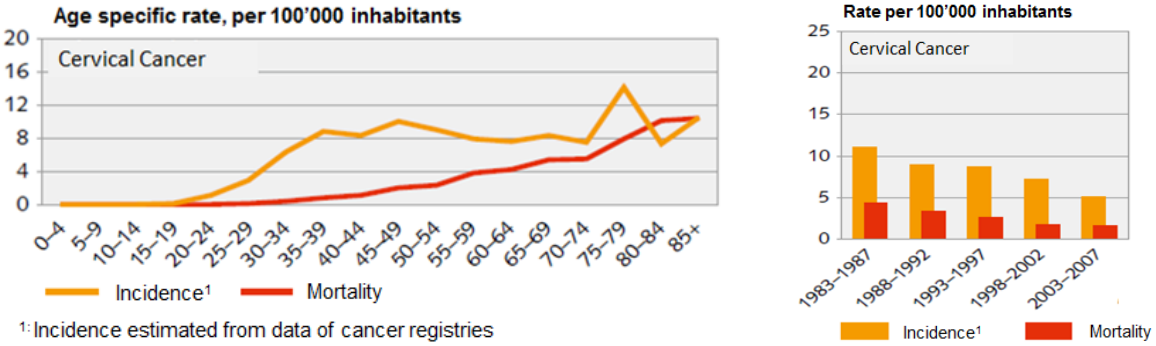
For women of 30 years and older, 5 yearly HPV testing with cytology triage or 5 yearly HPV16/18 genotyping with direct referral to colposcopy and cytology triage for other hrHPV types seem to be the screening strategies with the best balance of benefits and harms. In health economic studies, these strategies were either cheaper than cytology based testing or more expensive at incremental cost effectiveness ratios (ICERs) below acceptability thresholds. These findings are likely transferable to the Swiss health system. Feasibility analysis shows that the adherence to screening algorithms should be controlled to avoid overdiagnosis and overtreatment as well as loss to follow up. Therefore HPV based testing should be implemented preferably in an organized screening setting.

4 Introduction

4.1 Background and current status

In Switzerland 90 women die every year of cervical cancer and 240 fall ill with the disease. Cervical cancer makes up only 1.4% of all cancers of women in Switzerland, however in contrast to many other cancers about half of the women with the disease are younger than 50 years and a first peak in the incidence rate occurs between 35 and 39 years of age [20] (Figure 1).

Figure 1 Cervical Cancer in Switzerland adapted from figures G4.6.1 and G4.6.2 of [20]



In the last 30 years both the incidence and mortality of cervical cancer has steadily declined. This is attributed mainly to screening and early detection of precancerous and in situ cancerous stages with the help of the Pap test, named after its inventor George Papanicolaou. The test involves collection of cells from the cervix by a gynecologist and subsequent microscopic analysis for abnormal cells by a pathologist. The success of the screening is masking the comparatively high risk that cervical cancer is presenting to women's health: If the incidence of invasive cancers and that of in situ carcinomas detected by screening are combined, then the risk of developing cervical cancer is comparable to that of lung cancer (23/100'000 vs 25/100'000) [21]. Worldwide, cervical cancer is the fourth most frequent cancer in women with an estimated 530 000 new cases in 2012 and estimated 270'000 deaths representing 7.5% of all female cancer deaths. More than 85% of these cervical cancer related deaths occur in less developed regions [22].

In Switzerland regular screening for cervical cancer is recommended and the obligatory health insurance providers pay for a Pap test every 3 years. Even though screening with this assay is performed in Switzerland in an opportunistic manner and relies on the initiative of patients and gynecologists, approximately 50% of all women aged 25 to 55 who responded to the 2007 Swiss health survey declared to have undergone a Pap test within the last 12 months. Weaknesses of the opportunistic nature of the Swiss screening program are reflected in the difference to which degree persons of different cantons, nationalities and socioeconomic backgrounds participate [21].

The technological weakness of the Pap test is its low sensitivity. According to a US Study of 833 invasive cervical cancer cases in women enrolled in health plans revealed that 32% had had a negative Pap test in the previous 3 years [23].

In 2008 Harald zur Hausen received the Nobel Prize for the discovery that cervical cancer is caused by human papilloma viruses. Indeed HPV DNA is present in 99.7% of all cases of cervical squamous carcinomas [24]
Twelve to 15 HPV types are considered carcinogenic with HPV types 16 and 18 being the most aggressive [25] [26].

As a consequence of this discovery current prevention efforts are increasingly focused on the vaccination of young women against the HPV virus.

In addition the value of HPV testing for screening is under investigation. Several randomized controlled clinical trials have been initiated using tests for HPV infection to identify women at risk of developing cervical cancer. The most important trials are NTCC in Italy [12], POBASCAM in the Netherlands [16], Swedescreen in Sweden [19] and ARTISTIC in England [27].

Before HPV testing can be considered for screening programs a health technology assessment should be performed where potential clinical benefits and harms are weighed against each other, the optimal use of the technology is evaluated (e.g. frequency, combination with other technologies), and the cost-effectiveness of the new technology versus the current is calculated. The latter can be done as cost-effectiveness analysis (e.g. cost per life year saved, or cost utility analysis where costs per quality adjusted life years (QALYs) are calculated. Finally the feasibility of the alternatives needs to be assessed in the specific set up and technological and organizational resources available in a specific health system. (E.g. are both alternatives effective in an opportunistic versus organized screening program, and are all societal groups likely to benefit from the alternatives in the same way).

While a Health Technology Assessment (HTA) for Switzerland on HPV testing for cervical cancer screening is missing, HTAs exist for other countries e.g. the UK [2], Belgium [28], Australia [29] and Germany [30]. Cost-effectiveness analyses have also been published, e.g. in the Netherlands [31], Norway [32], Canada [33, 34] and the USA [35-37].

This master thesis addresses the gap of a missing HTA on primary testing with HPV for cervical cancer screening for the Swiss Health Care System by performing a systematic review of HTAs and health economic assessments of other countries. It assesses whether findings from these studies can be transferred to the Swiss environment and whether recommendations can be derived for the future of the Swiss screening set up for cervical cancer.

The conclusions of this thesis are expected to facilitate the discussion on the future of cervical cancer screening in Switzerland.

4.2 Hypotheses and Research Questions

Hypothesis 1

Cervical Cancer Screening can be improved both in terms of clinical effectiveness (due to better sensitivity of the HPV test, women at risk will be better managed and there will be fewer cases of advanced precancerous stages, fewer cases of invasive cancer and fewer deaths from cervical cancer), as well as in terms of cost effectiveness (due to longer possible intervals between screening visits for women testing negative), by using first line HPV testing instead of first line Pap testing.
The optimal test method may differ with the age of the screened subpopulation as women under 30 years of age have more transient HPV infections and lower incidence rates of cervical cancer than older women and may therefore suffer from more overdiagnosis and overtreatment with first line HPV testing than older women.

Research Question 1a

What is the best test or combination of tests which results in the highest clinical effectiveness to prevent cervical cancer at the lowest burden of follow up?

Research Question 1b

What is the best age to start using HPV as primary screening test in terms of clinical effectiveness and cost effectiveness?

Research Question 1c

How does the optimal algorithm for first line screening with HPV compare to the current regimen of cytological tests in terms of ICERs expressed as cost per modelled life year gained (LYG) or cost per QALY?

Hypothesis 2

Implementation of screening with first line HPV testing is feasible.
This aspect is important because a new screening technology may pose challenges with respect to organizational aspects, or acceptance by medical doctors and patients. It may create anxiety, increase inequalities by differential participation rates of social subgroups, or have side effects on other medical interventions or preventive actions by reducing the number of doctor's visits etc.

Research Question 2

In the event that HPV testing is found to be clinically effective and cost effective, are any potential barriers to implementing screening based on HPV testing identified? If yes, which barriers are these? Are they relevant for the Swiss health care setting?

5 Methods

Research questions 1a-c were addressed by a systematic review of the literature in the following steps.

1. Systematic reviews and meta analyses of clinical evidence were identified to get an overview of currently available clinical evidence. HTAs and health economic studies were identified to get an overview of health economic evidence.
2. Systematic reviews and meta analyses were analyzed for the research questions regarding evidence on clinical effectiveness of HPV testing.
3. HTAs and health economic studies were analyzed for the research questions in terms of clinical effectiveness and cost effectiveness. If the research questions were answered by an HTA or health economic study, it was further analyzed for its quality by application of the EURONHEED checklist [38]
4. and for its transferability of results to the Swiss health care system according to the criteria described below.
5. For studies that were found transferable to the Swiss setting, economic results were converted to Swiss currency of the cost year 2015 by adaptation to purchasing power parities.

Research question 2 was addressed as follows:

6. Those studies that identify screening with HPV as clinically and cost effective were analyzed for information on the feasibility of the implementation of the identified approaches and any potential barriers to implementation.

Synthesis:

7. In the final step the answers to the research questions were synthesized and considered for relevance for the Swiss Health System.

Details of these steps are described below.

5.1 Identification of relevant literature

PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and the databases of the University of York Centre for Reviews and Dissemination (CRD) http://www.crd.york.ac.uk/CRDWeb/, which include the Cochrane database, were searched with algorithms covering the following populations (P), interventions (I), comparators (C) and outcomes (O) (PICO):

P: Women undergoing cervical cancer screening.
I: Screening for cervical cancer with first line HPV testing.
C: Screening for cervical cancer with first line Pap test or Liquid Based Cytology (LBC).
O: For clinical results: precancerous stages detected, cancers prevented, cancer deaths prevented, LYG, QALYs
O: For health economic results: cost, ICER expressed as incremental cost per QALY gained or incremental cost per clinical effect parameter gained.

The search algorithm in PubMed was developed by combining MeSH items (Medical Subjects Headings) with keywords for all elements of the PICO. Thereby both indexed as well as non-indexed publications containing the elements of the PICO were included in the outcome of the search.
For the CRD database truncated keywords were used.
It was verified that the results with the search algorithms included already known relevant publications. In addition, the most recent relevant publications identified through the search, were checked for relevant references that might have been missed by the algorithms. The algorithms were refined until they found all publications already known or identified through the reference checks.

The full literature search algorithms are shown in Appendix 1: “Literature search algorithms”

Resulting titles and abstracts were screened for relevance to the research questions and publications meeting criteria underwent full text analysis. Publications not meeting criteria were excluded from further analysis.

The criteria for inclusion or exclusion of publications were the following:

- Publications were required to meet the PICO criteria.
- Only first line HPV screening was considered as intervention, e.g. studies that only assessed HPV testing as triage after positive Pap test were not considered.
- Only cytology based screening strategies (either with the Pap test or LBC) were considered as comparator.
- Only publications in English or German language were considered.
- Only economic analyses for industrialized countries (e.g. Europe, North America, and Australia) were considered in the analysis, as the transferability of health economic data from developing countries is unlikely.
- Only publications from 2008 and later were considered as the follow up of important randomized clinical studies such as NTCC [12], POBASCAM [16], Swedescreen [19] and ARTISTIC [27] ended in the years 2008 to 2012 [39]. Older publications are unlikely to reflect up to date current clinical effectiveness data.

- Only systematic reviews/ meta-analyses based on randomized controlled trials were used to assess clinical effectiveness.

- Exclusion criteria for publications that met criteria above were the following:
  - Only HPV testing based on samples taken by a clinician were included into the compilation of quantitative clinical and economic evidence. Publications evaluating the use of self-sampling in HPV testing were not analyzed in detail.
  - Publications were also excluded if they did not meet basic quality criteria for systematic reviews (e.g. no description of literature analysis, comments only).

- A four eyes principle was applied for the identification of relevant literature. In case of differences between the author of the thesis and the second person in the literature review process, the reasons for differences were discussed until agreement was reached for the selection or exclusion. The four eyes principle was only applied to the literature selection process. Extraction of answers to the research questions, evaluation of study quality and transferability were done by the author of this thesis alone.

The Prisma 2009 Flow Diagram [40] was used to document the literature selection process.

5.2 Analysis for evidence supporting research questions 1a-b

5.2.1 Definition of benefits and harms of screening with HPV testing

As a prerequisite for the evaluation of clinical effectiveness to prevent cervical cancer at the lowest burden of follow up, it is necessary to define the relevant indicators for clinical effectiveness (or benefits) versus burden from screening (or harms).

5.2.1.1 Measures of benefit

The most important measures of benefit are life years gained (LYG) or quality adjusted life years (QALYs) gained by a screening strategy. As surrogate markers the increased detection of precancerous stages in early screening rounds followed by decreased detection of those stages in subsequent screening rounds is considered a benefit.
The absolute sensitivity and specificity to detect precancerous stages are relevant measures as they influence the detection rate and the number of false positive results. The last investigated benefit measure is the length of time that a negative screening test can predict the absence of cervical cancer.

Cancer screening aims at the detection of cancer before symptoms arise. Earlier detection of cancer improves patient prognosis and can reduce mortality. Cervical cancer screening is especially attractive as precursor stages of cancer can be identified and treated which aims at the reduction of the incidence of cervical cancer [21].
Thus the ultimate benefits of cervical cancer screening are reduced morbidity and mortality from cervical cancer.
The related measures of benefit reported in this thesis are in most cases the number of life years gained or QALYs. Depending on the availability of data in the publications, cancer incidence rates, number of cancer cases and reduction of cancer risk may be shown. The findings on these benefit measures are shown in results chapters 7.1.1, 7.2.1, 7.3.1 and Table 10 in Appendix 4: “Research question 1a-c – Excerpt of answers from HTAs and Health Economic Studies”. Numbers on avoided cancer deaths were not available.

As the incidence of cervical cancer in countries with existing screening programs is low, surrogate markers such as the detection of precancerous stages are used to assess new strategies in clinical studies. Table 1 gives an overview of the nomenclature used for cytological and histologic findings during screening. Cervical Intraepithelial Neoplasia (CIN) of grade 2 and 3 are typically eligible for treatment to avoid progression to cancer. CIN3+ (the number of cases with CIN3 or invasive cervical cancer) seems the best surrogate marker as the probability of CIN3 to develop to invasive cancer is higher than that of CIN2 [41, 42].

Most meta analyses use the relative detection of CIN3+ and CIN2+ (the number of CIN2, CIN3 and invasive cancers) in a first screening round and reduced relative detection of CIN3+ and CIN2+ in a later screening round as markers of benefit [43-47]. The decreased detection in subsequent screening rounds is important as otherwise it could be argued that the additional precancerous lesions detected are predominantly those that would spontaneously regress if not detected and treated [12].
The relative detection (calculated as the ratio of detection of e.g. CIN3+ with HPV based testing versus cytology testing) is more independent of prevalence than positive predictive value (PPV) or negative predictive value (NPV) and thereby also better transferable to other countries with potentially different prevalence.

Therefore the surrogate marker related measures of benefits reported in this thesis are the increased detection of precancerous stages in early screening rounds followed by decreased detection of those stages in subsequent screening rounds.
Findings on the relative detection of CIN2+ and CIN3+ are described in the results chapter 7.2.2.

The last investigated benefit measure is the length of time that a negative screening test can predict the absence of cervical cancer. A screening test that allows longer reassurance against cancer will allow longer screening intervals and thus fewer screening events in a woman's lifetime. Fewer screening events also reduce the number of false positive results and avoid unnecessary treatments [48].
Findings that address the question on the possible length of time between screening rounds are described in results chapter 7.2.3.

5.2.1.2 Measures of harms

The most often reported indicators of the burden of screening are the rate of colposcopies done in a screening algorithm and increased cumulative detection of early precancerous stages over several screening rounds.

Harms from screening include anxiety from a positive screening result [49], inconvenience of more frequent and/or more intense follow up testing with colposcopies, as well as potential physical damage from biopsies taken during colposcopies and LEEP treatment of precancerous lesions [50] as cited in [51].

Depending on the clinical guidelines in different health systems CIN2 is treated by conization by Loop Electrosurgical Excision (LEEP) (e.g. in the US) [52] or rather observed for regression, persistence or progression (e.g. in Germany) [46]. In Switzerland the current expert letter on cervical cancer screening and follow-up [53] recommends treatment by

conization, except for pregnant women and for young nonparous (but screening compliant) women, where colposcopic surveillance every 6 months over 2 years is recommended. There are indications that LEEP treatments may result in an approximately two-fold increase in preterm delivery risk with risk increasing with the volume and numbers of excisions [54]. This association is currently challenged as the studies from which these data were retrieved involved comparatively large loop sizes and deep excisions [54] [28]. According to Bruinsma [55], the increased risk was observed only when women who underwent such procedures were compared with women with no history of abnormal cervical cytology or colposcopy results, while women with CIN may be at increased risk for preterm delivery even when untreated [54, 56]. Nevertheless, as long as this risk cannot be completely ruled out, special consideration needs to be taken to ensure that women of child bearing age are protected from these harms.
In the absence of data on the numbers of LEEP treatments the detection rates of precancerous lesions that are eligible for LEEP treatment (CIN2 and CIN3) were analyzed as a marker of potential burden.

While increased detection of CIN2+ and CIN3+ is a benefit if it occurs in earlier screening rounds and leads to lower occurrence of CIN3+ in later screening rounds, it may also indicate overdiagnosis.
It is known that not all of these lesions will progress to invasive cervical cancer. In a study in New Zealand a subset of women with CIN3+ lesions were not treated. As a follow up the incidence of cervical cancer was observed after up to 30 years [42]. 30% of these women had developed cervical cancer during this time. For CIN2 it is estimated that 40% regress over a period of 2 years with lower likelihood of regression for HPV16-positive CIN2 [41].

Therefore increased relative cumulative detection of CIN2+ and CIN3+ over several screening rounds is discussed in systematic reviews and meta analyses as a potential marker of overdiagnosis and thus potential harm [43, 45]. The results on this point are described in chapter 7.2.2.

In addition, the number of colposcopies can serve as surrogate marker for the potential burden of screening. This is the first more invasive screening activity and often involves biopsies. The number of colposcopies done in a screening program per woman screened, the relative rate of colposcopies between two screening strategies and the number of colposcopies done to detect one case of CIN3+ were frequently reported. Results on colposcopy rates of screening strategies are described in chapters 7.2.4 and 7.3.4.

5.2.2 Extraction of answers from systematic reviews and meta analyses

The information from systematic reviews and meta analyses on research questions 1a-b was extracted from the publications by making notes while reading each results chapter and by searching with key words per results chapter, e.g. “interval”, “year”, “length” for the chapter on evidence for the potential lengthening of screening intervals.

Some systematic reviews and meta analyses had a wider scope than this thesis and were evaluating other uses of HPV tests such as triage after a positive cytological test or follow up after treatment. In this case only the data regarding the use of HPV testing as a primary screening test were analyzed. If systematic reviews and meta analyses had information on

both screening in developed/ high resource versus developing / middle and low resource countries, only the analysis for developed / high resource countries was taken into account.

Results of the search were extracted and documented in Table 9 and Table 11. In addition a synthesis of all findings per result section was created by counting the systematic reviews, meta analyses, HTAs or health economic studies with similar findings (or no findings) and describing the key findings together with the references of the respective studies.

Clinical evidence from clinical systematic reviews and meta analyses and evidence on clinical and economic evidence from cost effectiveness models were first evaluated separately and afterwards a synthesis of findings from both was created by explaining similarities and differences.

5.2.3 Extraction of answers to research questions 1a-c from HTAs and health economic studies

The information from HTAs and health economic studies on research questions 1a-c were extracted with the same method as for clinical publications and are represented in Table 10 and Table 12

Extracted elements in Table 10 include a study description, the goal of the study, the country for which the analysis was performed, a brief description of the model (population, screening strategies modelled), the perspective of the economic evaluation, the currency and price year and the applied discounting rates for costs and benefits.
For research question 1a on the clinical effectiveness a short summary is provided stating how HPV based testing compared to cytology based testing in the model. In addition a tabular overview is provided of the clinical effectiveness data (life years or QALYs and if available % reduction of lifetime cancer risk or cancer incidence rate), for the most important strategies. (Typically all strategies that were on the cost effectiveness frontier are shown. In addition other strategies may be shown that are important for the comparison of different screening algorithms across studies). If available, data on the burden of screening (e.g. colposcopy rates) are shown. If not available a statement is made on the availability of these data.
For research question 1b on the best age to start testing for HPV, a summary of the findings of the study is provided. If the research question was not addressed, this is documented.
For research question 1c a summary statement is provided on the cost effectiveness of HPV based screening versus cytology based screening. Cost data were extracted in a table showing the costs and ICERs for the strategies. If no ICER values were provided in the studies, the dominant strategies were identified from the cost effectiveness plane in the study and the ICERs were calculated based on the LYG (or QALYs) and cost data provided. In this case some inaccuracy of the ICER values occurs due to rounding effects (as both costs and LYG will not be displayed in the publication with all available positions after the decimal point). In this case this is annotated in the applicable table.

5.2.4 Terms used to characterize strategies from an economic perspective

The term “dominant” is used for a strategy that was shown to be more effective and less costly than another. Vice versa a strategy is said to be “dominated” either because it was

less effective and more costly than another or when it was less costly than another, but had a higher incremental cost-effectiveness ratio ("weakly dominated").
Strategies that were not dominated by any other strategy are considered to be on the "cost-effectiveness frontier". Strategies are considered "cost-effective", if they were on the cost-effectiveness frontier and did not exceed an absolute country specific threshold for their incremental cost effectiveness ratio as discussed below.

5.3 Evaluation of the quality of HTAs / health economic studies

The analysis of the quality of studies can be supported by using checklists.
The systematic review of Goeree et al [57] on the transferability of HTAs and economic evaluations compared different checklists for the evaluation of the quality and availability of transferability information of publications. Of these, the checklist of Boulenger was selected (hereafter called the EURONHEED checklist) [58], together with the guidelines to complete the list [38] to evaluate the publications for this thesis. The advantage of this checklist was that the general quality of the publication could be assessed in a systematic manner as well as the availability of data for the transferability analysis.

The EURONHEED checklist [38] is shown in Table 13 and consists of 6 main sections:

- Questions Q1–M2 aim at the quality of description of the research question, the PICO elements and the inputs of studies (samples) or models (e.g. detail of description, origin of model parameters).
- Questions E1–E7 aim at the detail and quality of clinical effectiveness reporting.
- Questions B1– B5 address the definition and valuation of benefits measures (e.g. QALYs).
- Questions C1–C11 cover the level of detail on costs inputs.
- Questions D1– D4 cover discounting aspects
- Questions S1 and O1 address important aspects of the discussion by the authors.

The full checklist contains 42 questions. 16 of these (shown in Table 13 in bold and blue background color), are specifically aimed at important data for the evaluation of transferability.
For each question the following answers are possible and are assigned a score as indicated in ():

- 'yes' (1),
- 'partially' (P) (0.5),
- 'no or no information provided' (No/NI) (0), or
- 'not applicable' (N/A).

To calculate the quality data score all 42 questions are used and for the calculation of the transferability data score only the subset of 16 questions are used.
The scores are calculated with the formula:

$$\Sigma_i S_i / n–x.$$

where n is the number of questions, x is the number of questions for which the response is N/A and S is the score of each question.

The maximum score possible is 1 if all applicable questions are answered with a 'yes'.

The value of the quality data score is indicative of the level of detail provided on all important aspects of a study. No weighting in the score of single different questions is applied. Therefore a “no” to a fundamental quality criterion such as HT1 and HT2 (description of intervention and comparator in sufficient detail), or E5 (adequate reporting on the effectiveness results), is weighted equally to ‘no’ in Q2 (justification of the alternative technologies used by the author). However the authors of the checklist state that weighting is applied in the checklist by having several detailed questions on important aspects of study quality [38], so that publications of minor quality still result in lower scores than studies of higher quality.

In addition Goeree et al. recommend to define “knock-out” criteria for the quality of a publication, based on a subset of questions [57]. In the case of this thesis a “no” to the question E5 (adequate reporting on the effectiveness results) was considered a knock-out criterion from a quality perspective.

The value of the transferability data score is indicative of how much detail is provided that can be used for the transferability analysis of a study (and thus is not indicative for the result of the transferability analysis).

The results for all single questions of the checklist for the health economic studies are provided in Table 13. The quality data score for each study is also provided in Table 10.

Wherever the checklist showed that relevant information is missing or incomplete and this might have influenced the results, this was made transparent when results of this study were reported in the results section.

To evaluate whether results were influenced by the study quality, a comparison was done, whether certain screening strategies were only analyzed by studies with low or high quality data scores, or whether the quantitative effects (ICERs) correlated with the quality data scores. This was only done for studies that were found to be potentially transferable

5.4 Evaluation of the transferability of health economic results to the Swiss health care system

The transferability of answers to the research questions from each health economic study to the Swiss health care system was analyzed based on the following criteria (adapted from the approach Michael Drummond taught in the 2014 Lugano summer school on HTA Assessments):

- Was a comparator used that is relevant to the current Swiss setting? Is the viewpoint of the analysis relevant to the Swiss setting?
- Do treatment options used in the model compare to current clinical practice in Switzerland?
- Is there any indication of a different base line risk of the populations?
- Does the screening setting (organized or opportunistic) influence the result?
- Can results of the sensitivity analyses be used to make assumptions for the Swiss setting? If any parameters are different in the Swiss setting, have they been analyzed in the sensitivity analysis? If yes, are the differences expected to influence the result of the research question and in what direction?

- Can costs and consequences be deduced for the Swiss setting (e.g. by putting Swiss units and costs into the calculation of the study or by adaptation to purchasing power)?

After all aspects had been assessed a summary statement was created for the transferability of each study.
The algorithm applied was:

1. Studies with insufficient level of reporting were excluded from further transferability analysis based on a rating in the EURONHEED checklist with 'No/NI' of questions E5 (adequate reporting on the effectiveness results).
2. Studies not containing a comparator relevant for the Swiss health system were not considered transferable.
3. All other studies were considered potentially transferable and any differences observed from the Swiss setting or the impact of study reporting weaknesses were assessed based on the detailed analyses according to the steps below.

The exclusion criteria are in line with the knock-out criteria applied by Welte et al. in their transferability decision chart [59].

The results of this analysis are presented in Table 14.

In order to analyze transferability, reference values for the Swiss Health System were identified as described in the following sections:

5.4.1 Was a comparator used that is relevant to the current Swiss setting?

A relevant comparator for the Swiss setting should be as close as possible to current practice in Switzerland. In the absence of data that systematically monitor the actual implementation of cervical cancer screening in Switzerland the recommendations of the Swiss Society for Gynecology and Obstetrics and the reimbursement rules of the obligatory health insurance system were assumed to be representative of current practice.

The Swiss Society for Gynecology and Obstetrics recommends cervical cancer screening in Switzerland with a cytological test every 3 years for women aged 30-70 and every 2 years for women of 21-29 years in the "SGGG Expertenbrief 40" [53]. The obligatory health insurance system grants reimbursement for the first two screening tests with a yearly frequency and afterwards for a test every three years. Both Pap test and liquid based cytology are used in Switzerland for cervical cancer screening [1]. After a cytological primary screening result of atypical squamous cells of undetermined significance (ASC-US), an HPV test is recommended (see 0 for details).
Therefore the Swiss recommendations for screening algorithms are most similar to the strategies "cytology with HPV triage" used in health economic modelling studies with a 3-yearly frequency.

Another aspect of the comparability of the screening is the assumed sensitivity and specificity for the screening tests. Studies in Germany have shown that the sensitivity of Pap testing in Germany was much lower than in international studies, partly due to the practice of sampling by gynecologists [60]. No Swiss reference data are available for this aspect of the transferability analysis, as no published data on the actual sensitivity and specificity of cytological screening in Switzerland were found. Sensitivities and specificities in the transferability analysis are therefore described in Table 14 but not specifically discussed.

5.4.2 Is the viewpoint of the analysis relevant to the Swiss setting?

The viewpoints taken in the different studies were typically the healthcare payers perspective and always included direct medical costs. Indirect medical costs (e.g. women's travel cost to screening, diagnosis and treatment and productivity loss of women due to participation in screening, diagnosis and treatment for cancer and precancerous lesions) were sometimes also included. In countries with organized screening, costs for the organization of the screening program including invitations, reminders and registrations of screening results were also included.

In this thesis all viewpoints in the different studies were considered potentially relevant for the Swiss setting. Even where costs of an organized screening program were included, this viewpoint may become relevant in the future should Switzerland decide to implement an organized screening program for cervical cancer. This is currently being discussed as part of the Swiss national strategy against cancer [61]. In this case it will be important to know how cost effective HPV based testing will be compared to cytology based testing under that setting.

As the viewpoint and thus the included costs can influence the total cost of screening and thus the height of the ICER, for transparency and better comparability the viewpoint taken and included costs are described for each study in Table 14.

5.4.3 Do treatment options used in the model compare to current clinical practice in Switzerland?

The Swiss Society for Gynecology and Obstetrics recommends the following algorithms of positive cytological and histological findings in the "SGGG Expertenbrief 40" [53] (Table 3).

Table 3: Recommended follow up and treatment of screening results in Switzerland

Cytological screening test result	**follow up**
LSIL	Colposcopy indicated. If negative repeat cytology after 6 and 12 months.
HSIL	Colposcopy, cytology and biopsy. Diagnostic conization if result is ambiguous (for women <30 years postpone conization if compliance with follow up is high. In this case colposcopy and cytology after 6 and 12 months.
ASC-US	HPV test. If HPV negative repeat cytology after 6 and 12 months. If HPV positive perform colposcopy, cytology and biopsy.
ASC-H (atypical squamous cells)	Colposcopy
AGC (Atypical Glandular cells of Undetermined Significance)	Colposcopy, endocervical curettage and HPV typing If all results negative, colposcopy every 4-6 months for 2 years.
Histological Finding	**Follow up**
CIN 1	Cytology every 6 months. If CIN1 is persistent over 2 years or if cytology and histology are discrepant, conization or laser vaporization
CIN 2-3	Conization if woman is not pregnant. In young nulliparous women who are compliant with follow up screening: colposcopy and cytology every 6 months for 2 years. If persistent after 2 years conization
AIS (Adenocarcinoma in Situ)	Deep conization with curettage of endocervix.

In the transferability analysis treatment options described in the health economic models were compared to Swiss recommended treatments. If differences were observed these were discussed for their potential impact on the transferability of the results.

5.4.4 Is there any indication of a different base line risk of the populations?

A different base line risk of the population may be relevant for transferability as models are "calibrated" to a country specific cancer incidence rate and / or a HPV prevalence rate. Therefore all health economic studies were compared for the comparability of those rates. If differences were found, they are discussed for their potential relevance on the transferability of the results in Table 14.

The epidemiology of cervical cancer in Switzerland was partly described in the introduction. Compared to other developed countries the age corrected incidence and mortality of cervical cancer is low. The latest published data from 2008-2012 of the Swiss National Institute for Cancer Epidemiology and Registration (NICER) (http://www.nicer.org/NicerReportFiles2015-2/EN/report/atlas.html?&geog=0, last accessed Jan 05 2016), show an age standardized

incidence rate per 100'000 women of 5.4 (95% CI = 4.9-5.8) and an age standardized mortality rate per 100'000 women of 1.4 (95% CI = 1.2-1.5).

Swiss HPV prevalence values were taken from de Vuyst et al [62] who compared age dependent prevalence of hrHPV between several European countries. Swiss prevalence values in women between 30 and 60 years were found slightly above mean prevalence (9.4% vs 8.1%). In younger women below 30 years Swiss prevalence values were lower than in most other analyzed countries.

5.4.5 Does the screening setting influence the result?

In this thesis it is assumed that the screening setting (e.g. organized or opportunistic) will mostly influence the attendance rates of women in primary screening and follow up.

Therefore in the transferability analysis modelled attendance rates were extracted from the health economic studies and compared to attendance rates in Switzerland.
If differences were observed they were discussed for their potential impact on transferability.

The Swiss reference values for screening coverage and attendance rates can only be estimated. In Switzerland organization of cervical cancer screening is opportunistic and mostly depends on the recommendations of gynecologists and general practitioners. As there is no central organization and quality assurance of cervical cancer screening there is neither systematic monitoring nor control over the implementation of the screening recommendations.
Estimations by the Swiss Federal Office of Public Health (BAG) indicate that there is overscreening in some women and other women are never or rarely screened [1].
Both underscreening of a significant number of Swiss women as well as overscreening is further implied by the results of the Swiss Health Survey 2007 as portrayed in [21].
79.6% of the women (20 years and older) reported that they had had a cervical cancer screening test at least once in their lifetime. These data indicate that 20% of the women in Switzerland never participate in cervical cancer screening.
Overscreening compared to guidelines is indicated by the number of women reporting that they had a cervical smear within the last 12 months (42.5% across all age ranges), with the highest numbers reported by women between 30 and 49 (about 52%). If women of this age group were tested every three years according to guidelines, only 33% should have been tested within the last 12 months. Therefore these numbers indicate more frequent testing of a significant number of women. A cost effectiveness analysis of 2008 for the addition of HPV vaccination to cervical cancer screening in Switzerland [63] assumed a real life frequency of screening of every 2 years based on expert opinions.

In addition to attendance of women, the compliance of physicians to recommended follow up procedures may be higher in organized screening programs than in an opportunistic setting. No recent data were found for Switzerland for compliance to cervical cancer screening follow up and treatment recommendations. Therefore baseline data for a comparison are not available and a discussion of this aspect impossible.

5.4.6 Can results of the sensitivity analyses be used to make assumptions for the Swiss setting? If any parameters are different in the Swiss setting, have they been analyzed in the sensitivity analysis? If yes, are the differences expected to influence the result of the research question and in what direction?

If any differences were identified for aspects 5.4.1 to 5.4.5, it was checked if the aspect was addressed in the sensitivity analysis of the study and was found to have an impact on the results. This information contributed to the evaluation of the points 5.4.1 to 5.4.5 as described above.

5.4.7 Can costs and consequences be deduced for the Swiss setting (e.g. by putting Swiss units and costs into the calculation of the study or by adaptation to purchasing power?)

If the studies did not provide results in a manner that allowed putting Swiss units and costs into the calculation of the study, the costs and ICERs were deduced by adaptation to purchasing power parities was pursued.
For studies which were found to be potentially transferable to the Swiss Health System it was analyzed how ICERs calculated in different local currencies for different cost years might translate into Swiss Francs (CHF) for the same cost year (2015). It is clear that such a translation will only lead to an approximation of the true costs in Switzerland. However this translation at least improves comparability of the different studies and gives an impression of where the ICERs would be in CHF/LYG or /QALY.

A comprehensive method for conversion of cost factors from one country to another would involve adaptation to three factors: differences in resource utilization, differences in prices of healthcare services and changes in costs over time. (Personal communication of Matthias Schwenkglenks). However, for the research questions in this thesis an adaptation to resource utilization was not deemed applicable, as the different screening strategies used in the models have inherent fixed assumptions for resource utilizations. Adaptation to prices of healthcare services was done by applying purchasing power parities and changes in costs over time according to the description below.

If costs were reported in the original currency of the country, the cost values were directly translated into CHF with the conversion factor for the Organization for Economic Co-operation and Development (OECD) Purchasing Power Parity (PPP) values from http://stats.oecd.org/Index.aspx?DataSetCode=PPPGDP last accessed March 20, 2016. Afterwards the value in CHF was inflated to 2015 by using the annual average Swiss consumer price index rates from http://www.bfs.admin.ch/bfs/portal/de/index/themen/05/02/blank/key/jahresdurchschnitte.html; last accessed March 24, 2016.
If costs were reported in another currency and the conversion factor to local currency was reported, the costs were reconverted with that factor to local currency before converting to CHF with PPPs.
If costs were reported in another currency and no conversion factor was given, the costs were reconverted to local currency by using a conversion factor from the year the costs were reported. The conversion factor was taken from http://www.wallstreet-online.de/waehrungsrechner for July 1st of the cost year. In this case the conversion factor is reported in the thesis.

5.4.7.1 Cost of screening tests in studies compared to Switzerland

As the sensitivity analyses of studies showed that the assumed costs of the cytology and HPV assay influences the costs and ICERs within a study, the current costs of these tests in Switzerland have been investigated.
According to 2012 Tarmed tax points and with the Canton of Zürich as example a Pap test is reimbursed with 20.30 CHF if negative, 40.20 CHF if ambiguous and 71.70 CHF if positive. HPV hybridization (which is one method of HPV triage of positive cytological tests), is reimbursed with 84.76 CHF.
There is no price (tax point) fixed for hrHPV testing as a primary cervical cancer screening test, as this is not a reimbursed screening strategy. However, in the "Analysenliste" a maximum reimbursement of 180 CHF is given for HPV DNA Amplification and hrHPV typing. Should HPV testing become a primary screening test in Switzerland a new price will have to be fixed for this application. This price will likely be lower than the current value in the "Analysenliste" due to higher expected testing volumes.

5.4.7.2 Accepted ICER threshold of a cost effective intervention in Switzerland

There is no published accepted ICER threshold in Switzerland. The World Health Organization's (WHO) Commission on Macroeconomics and Health recommends that an intervention be considered very cost-effective if the ICER is less than the country's per capita gross domestic product. (World Health Organization, Macroeconomics and Health: investing in health for economic development: report of the commission on macroeconomics and health; 2001).

The provisional per capita Gross Domestic Product (GDP) 2014 for Switzerland according to the Federal Office of Statistics is 78'432 CHF
http://www.bfs.admin.ch/bfs/portal/de/index/themen/04/02/01/key/bip_einw.html last accessed 24 Jan 2016.
In a decision of the Swiss Federal Court (BGE 136 V 395) a limit of 100'000 CHF/ LYG was deemed an acceptable threshold.

Therefore, in the discussion of the potential cost effectiveness in a Swiss setting, ICER values translated into 2015 CHF were compared to an acceptable threshold of 100'000 CHF/LYG. In studies where only cost/ QALY were shown, an acceptable threshold of 100'000 CHF/QALY was assumed. As cost per QALY is always the same or higher than cost per LYG within the same study, this seemed an acceptable simplification.

5.4.8 Were QALYs evaluated likely to be the same in Switzerland?

The original checklist of Drummond also contains the question whether QALYs evaluated in a study would likely be the same in the country of interest. However Swiss baseline data for QALYs of all aspects of cervical cancer screening are not available. Only some disutilities have been used for cervical cancer stages in a Swiss study on the cost effectiveness of HPV vaccination [63]. Therefore, this aspect was not taken into account for the decision whether a study was transferable or not. If QALYs were used in a study they are described in Table 10 and Table 5. The effect of using different sets of disutilities for the creation of QALYs is discussed in chapter 7.3.4.3**Error! Reference source not found.**.

5.5 Extraction of answers to research question 2

All clinical and economic studies were analyzed for information on the feasibility of the implementation of the identified approaches and any potential barriers to implementation.

During the analysis of the publications for the other research questions notes were taken on contents addressing research question 2. In a second step, to ensure that a systematic approach was taken, all publications were searched with the terms “concern”, “feasib”, “barrier”, “implement” and “however”. Publications in German language were searched with the terms “bedenken”, “durchführ”, „einführ“, “möglich”, “machbar”, “hinder”, “implement”, “umsetz”, “trotzdem”, “hingegen”, “dennoch”, “allerdings”, “jedoch” und “aber”. By this method paragraphs containing concerns on the implementation of HPV based screening were identified that could have been missed in the first step.

Answers were then classified into “concern categories” and focus areas identified based on the frequency that the different concerns were mentioned. All detailed information retrieved and the associated concern categories are displayed in Appendix 5: “Research question 2 – Excerpt of answers”.

Relevance for the Swiss health system was assessed by comparing the concerns to available information on the Swiss cervical cancer screening set up.

The areas of concern are described in results chapter 10.1 and the relevance for the Swiss health system is described in chapter 10.2.

5.6 Conclusions for Swiss policy

Based on the findings for Research Questions 1a, b and c and 2, hypotheses 1 and 2 are answered and a recommendation for Swiss policy is made.

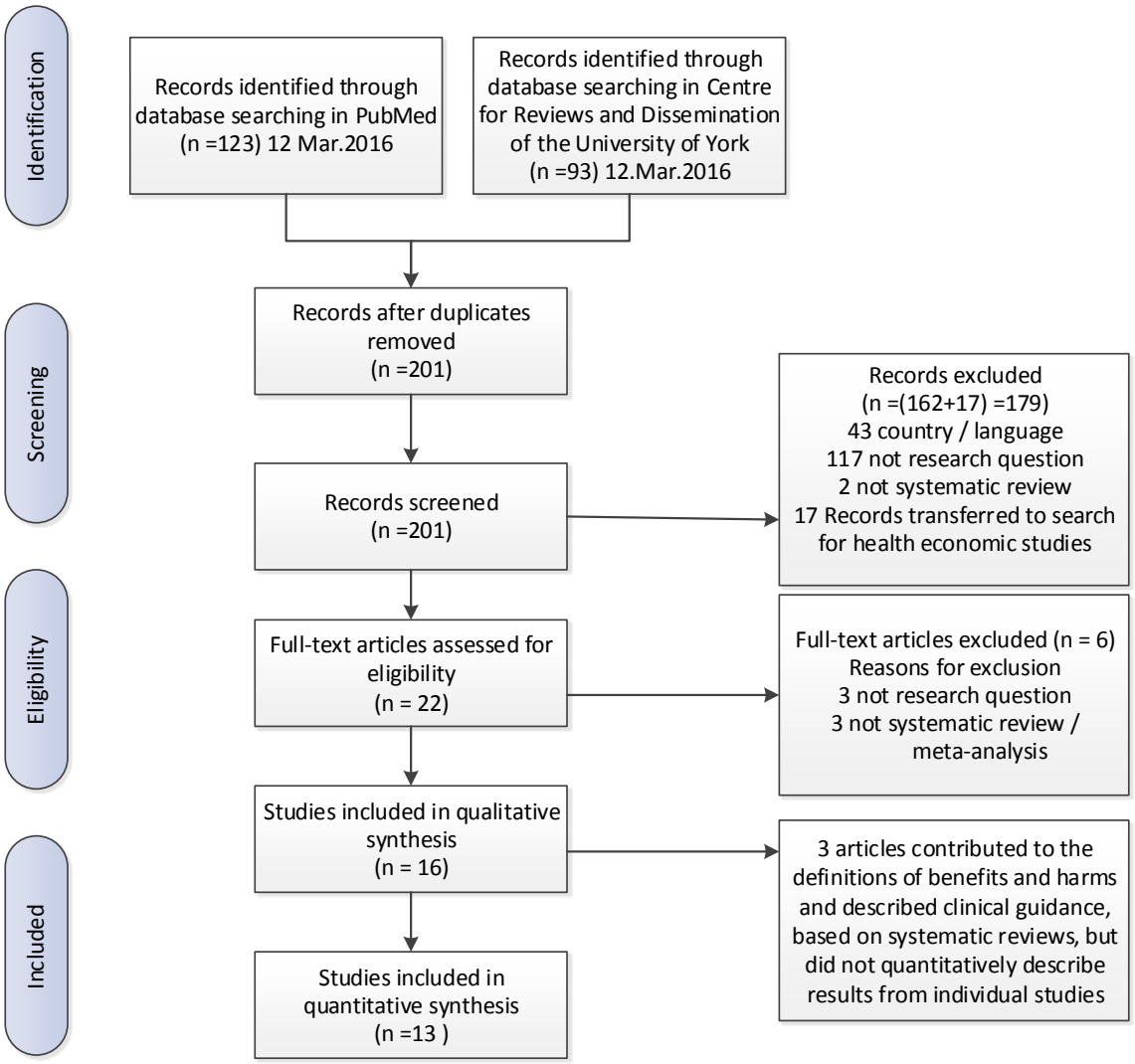
6 Literature Search Results

6.1 Literature search results Clinical Systematic Reviews and Meta Analyses

Figure 2 shows the Prisma 2009 Flow Diagram for the literature selection of clinical systematic reviews or meta analyses. The last search of the databases was done on March 12, 2016. After removal of duplicates 201 publications remained. The titles and abstracts of these publications were screened for relevance to the research questions and the exclusion criteria described in the methods chapter. Seventeen records were health economic studies and analyzed in the health economic evidence results. 179 records were excluded based on titles and abstract search. The remaining 22 publications underwent full text search and another 6 articles were excluded. Reasons for exclusion were in 43 cases that language or countries did not meet inclusion criteria, in 120 cases that publications did not address the research questions (many publications covered HPV vaccination instead of primary cervical cancer screening with HPV tests), and in 5 cases that publications were not systematic reviews or meta analyses (e.g. short comments or reviews that were explicitly identified as not being a systematic review).
Sixteen systematic reviews and meta analyses remained that were further analyzed for this thesis [43-49, 51, 52, 54, 56, 64-68].
Seven of these were done from the perspective of the US health system [64] [54] [56] [51] [67] [52, 68], 2 from the perspective of the German health system [46, 65] (one being an update of the other), and 7 studies were done independent of a specific health system [43] [47] [66], [44] [48] [45] [49]. Analyses related to a specific health system were typically done to develop new clinical guidelines, while the other studies typically aimed at a comparison of the relative sensitivity and specificity of HPV based versus cytology based cervical cancer screening.

Of three studies only qualitative results including the definition of benefits and harms of different cervical cancer strategies were derived [51, 52, 56].

Figure 2 Prisma 2009 Flow Diagram [38] for search results for clinical systematic reviews or meta analyses



6.1.1 Evolution of Clinical Evidence - Relevant clinical studies

The randomized controlled studies POBASCAM, Swedescreen, NTCC1, NTCC2 and ARTISTIC and their combined follow up, are considered the key randomized controlled studies in the evolution of clinical evidence about HPV based cervical cancer screening. In addition the cohort studies KPNC, VUSAscreen and ATHENA had relevant influence on the formation of new clinical guidance.

To analyze the clinical evidence, systematic reviews and meta analyses from 2008 onwards were searched. As since 2008 several key clinical studies were still ongoing and more and more results were published, earlier reviews and meta analyses come partially to different conclusions than more recent publications, depending on the amount of information available at the time of writing.

To illustrate how clinical information emerged within the last years a brief summary of the evolution of clinical evidence is provided below. An overview of study setup and results of individual studies included into systematic reviews and meta-analyses is provided in Appendix 2: “Description of Randomized Controlled Trials and Cohort Studies”.

6.1.1.1 Background

As cervical cancer screening with the Pap test has successfully reduced cancer incidence and mortality in countries where screening was established [49], researchers exploring the use of HPV testing in cervical cancer screening had to find a balance to gain data on potential benefits and harms for HPV testing without putting women in the intervention arm of the study at risk of higher cancer morbidity and mortality.
First studies were therefore cross sectional and cohort studies to evaluate the statistical association of positive HPV and cytology tests and the prevalence and subsequent incidence of cervical cancer precursors and invasive cervical cancer cases as summarized in the systematic review of Cuzick from 2008 [49].

6.1.1.2 Studies with HPV and Cytology Cotesting in the Intervention Arm

Based on the data from cross sectional studies and cohorts the first randomized controlled trials were performed in Europe which contained an intervention arm of cotesting of HPV and cytology tests. These studies are POBASCAM in the Netherlands (end results reported in 2012 [16]), Swedescreen in Sweden (end results reported in 2009 [18], follow up results reported in 2014 [69]), ARTISTIC in the UK (end results published in 2009 [3], follow up until 2014 included into the UK HTA of 2014 [2]), and NTCC 1 in Italy (end results published in 2010 [12]).

6.1.1.3 Studies with HPV testing only in the intervention arm

Comparing data on women with both a negative HPV and negative cytology test with women with only a negative HPV test revealed, that an additional cytology test adds only little sensitivity and therefore allowed the first clinical studies in which women in the intervention arm received only a standalone HPV test in the first screening round (NTCC 2 in Italy) or HPV testing with cytology triage (FPHT in Finland).

One study frequently included into systematic reviews and meta-analyses even though not transferable to a European or US context, is a study done in rural India ("INDIA" [70]) where a previously unscreened population was either screened with one time HPV testing or one time cytological testing. The study showed that one time screening with HPV testing significantly reduced morbidity and mortality from cervical cancer compared to unscreened women, while one time screening with cytology screening did not. Some systematic reviews and meta-analyses [44, 46] included this study to compare relative detection rates of cervical cancer and precancerous stages in a first screening round.

6.1.1.4 Cohort studies addressing HPV based testing with and without partial genotyping

The women participating in the studies POBASCAM, Swedescreen, NTCC and ARTISTIC were followed up in a combined cohort study published in 2014 [39].

Other important cohort studies include VUSAscreen in the Netherlands(end results published 2012 [71]), and the huge US KPNC Study. In the latter the follow up of up to 1.4 million American women screened by cotesting with HPV and cytology is analysed (end results published 2014 [11, 72, 73].
The most recent systematic review of Huh et al. [64] also included the industry sponsored ATHENA study which characterizes a new HPV test yielding results in one measurement for all hrHPV types and for HPV 16 and 18 thus allowing triage of HPV positive women by HPV subtyping (end results published 2015 [5]).

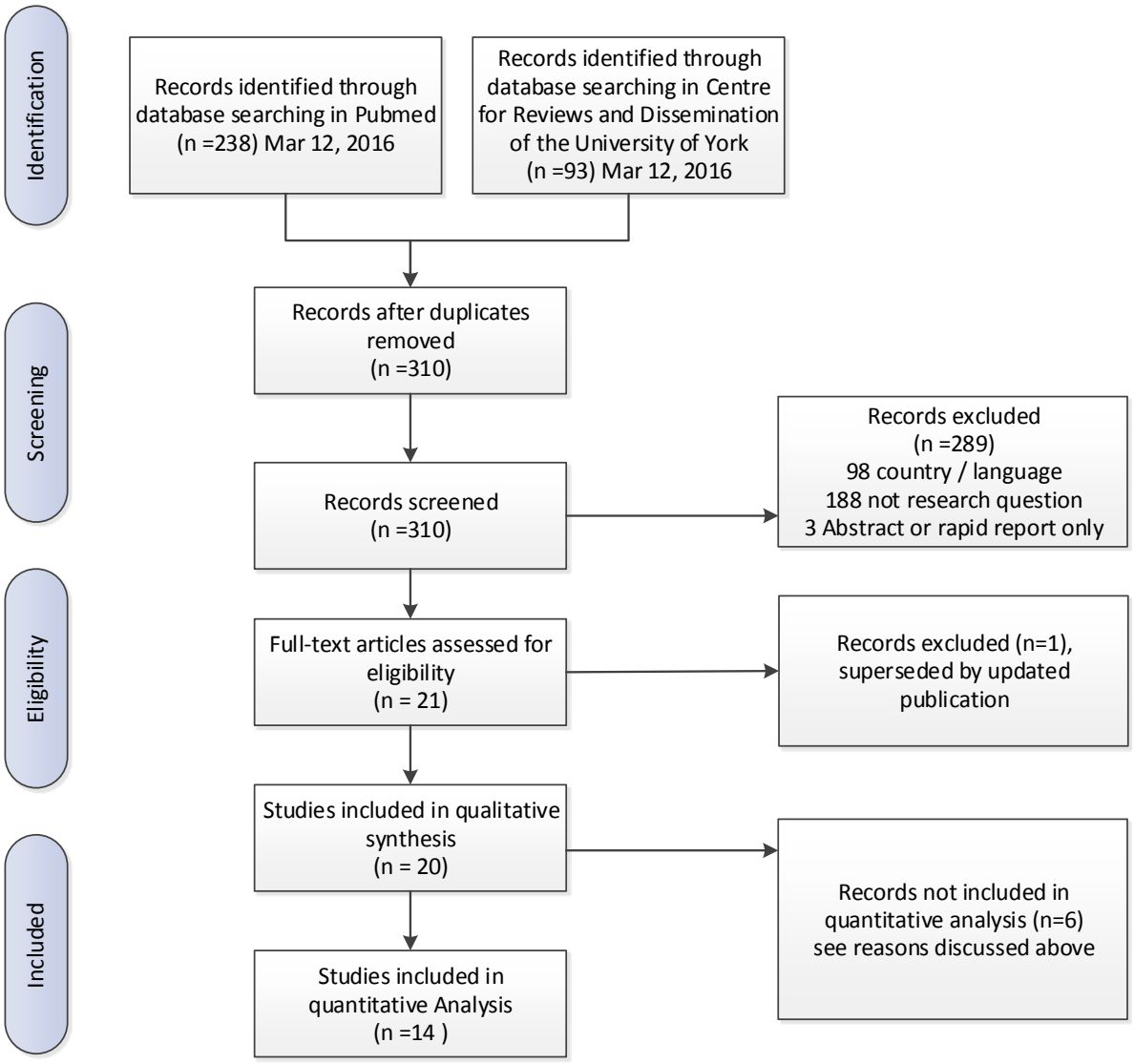
6.2 Literature Search Results HTAs and Health Economic Studies

Figure 3 shows the Prisma 2009 Flow Diagram for the literature selection of HTAs and health economic studies. The last search of the databases was done on March 12, 2016. After removal of duplicates 310 publications remained. The titles and abstracts of these publications were screened for relevance to the research questions and the exclusion criteria described in the methods chapter. 289 records were excluded based on titles and abstract search. The remaining 21 publications underwent full text search and 1 other article was excluded [3] because it was superseded by a newer publication on the topic of the same authors [2].
Twenty studies were found that were included in the qualitative analysis [2, 28-37, 60, 74-81].

Six publications did not give results for the quantitative and/ or transferability analysis.
The studies of Dillner and Mühlberger [74, 81] were reviews of primary health economic studies and did not yield quantitative results, however qualitative input was available e.g. on research question 2. Two studies did not report results in sufficient detail for quantitative analysis [77, 78]. The studies of Berkhof and van Rosmalen [31, 79] did not include or show results for a comparator of 3 yearly screening (the minimum frequency was 5 yearly), and therefore allowed no transferability analysis to the Swiss setting.

The included publications are health technology assessments from Belgium [28], the UK [2], Germany [30, 60] and Australia [29] and health economic studies from the USA [35-37], Canada [33, 34], Italy [76], Norway [32] and Sweden [75].

Figure 3 Prisma 2009 Flow Diagram [38] for Search Results for Health economic Studies



7 Results Research Question 1a "What is the best test or combination of tests which results in the highest clinical effectiveness to prevent cervical cancer at the lowest burden of follow up?"

The results chapter starts with a summary of all key findings (7.1), then describes the details from clinical systematic reviews and meta analyses (7.2), followed by the details extracted from HTAs and health economic studies (7.3). A reference is given after the summary statements to the subsequent chapters where detailed results and references to publications can be found.

7.1 Summary Results Research Question 1a

7.1.1 Protection against cervical cancer

Evidence from both clinical studies and health economic studies showed that HPV based cervical cancer screening is more effective than cytology based screening in preventing cervical cancer cases. (7.2.1, 7.3.1)

7.1.2 Surrogate Markers CIN2+ and CIN3+ over 2 screening rounds

Meta analyses of Randomized Clinical Trials (RCTs) showed that HPV based testing leads to increased detection of CIN2+ and CIN3+ in the first screening round and decreased detection in the second screening round (7.2.2).
Comparison of CIN2+ and CIN3+ over 2 screening rounds from RCTs indicates that direct referral to colposcopy after a single HPV positive result leads to overdetection of CIN2 and CIN3 lesions that might otherwise regress without being detected.
On the other hand strategies that used HPV testing with cytology triage and retesting to detect HPV persistence before colposcopy referral did not lead to increased CIN2+ or CIN3+ numbers over 2 screening rounds. This was interpreted by most systematic reviews as proof of earlier detection of precancerous lesions instead of overdetection of regressive lesions in the first screening round. One systematic review disagreed with this interpretation and 1 was not sure how to interpret this finding.
Detection of precancerous lesions was not discussed in health economic studies. However 3 studies used QALYs instead of life years as effectiveness markers and assigned disutilities to precancerous lesions. In these studies HPV based screening strategies were more effective in terms of QALYs than cytology based screening strategies (7.3.4.3).

7.1.2.1 Sensitivity and specificity of HPV versus cytology based screening

HPV testing was 24 to 40% more sensitive but 2-8 % less specific than cytology tests to detect precancerous lesions CIN2+ or CIN3+ as shown by a meta analysis based on RCTs and cross sectional studies (7.2.2.4).

7.1.3 HPV testing with direct referral to colposcopy

HPV testing with direct referral to colposcopy showed higher clinical effectiveness than cytology based testing based on the RCT NTCC and health economic models (7.2.2.2, 7.3.1). However HPV testing with direct referral to colposcopy seems also to increase the detection of lesions that might otherwise regress before detection. In addition both systematic reviews as well as health economic studies show that this strategy leads to approximately twofold increased colposcopy rates (7.2.2.3, 7.2.4.1, 7.3.4.1).

7.1.4 HPV with cytology triage

HPV with cytology triage showed higher clinical effectiveness than cytology based testing based on RCTs and all health economic models that were included into the analysis (7.2.2, 7.2.4.1, 7.3.1, 7.3.4.1).

Whether or not colposcopy rates are increased compared to cytology varied between studies. One systematic review found lower colposcopy rates with HPV versus cytology testing in the RCT FPHT and 10-20% higher colposcopy rates in POBASCAM and ARTISTIC. Another systematic review calculated colposcopy rates per detected CIN3+ and found elevated colposcopy numbers (5.4 vs 4) in ARTISTIC and NTCC1, however not in POBASCAM and FPTH. The combined follow up of POBASCAM, NTCC, ARTISTIC and Swedescreen showed that the number of women with biopsies were comparable in the strategies applying HPV with cytology triage algorithms (7.2.4.1).

Colposcopy rates of HPV based screening were lower with HPV based testing when longer screening intervals were used:

Three models cited in systematic reviews showed that colposcopy rates with 5 yearly HPV with cytology triage are lower than with 3 yearly cytology based testing (7.2.4.2).

Four health economic studies modelled colposcopy rates for HPV with cytology triage and found that these rates were slightly lower or slightly higher than with cytology based screening (-4% to + 10%). In these studies screening frequencies of HPV based testing were closer to those of the cytology based screening (3 yearly in 2 of these studies and in the other 2 studies cytology based screening was done at 5 yearly intervals at the age of 50-65 (7.3.4.1)).

7.1.5 Cotesting

Cotesting showed higher clinical effectiveness than cytology based testing based on RCTs and all health economic models that had modelled this screening strategy (7.2.1, 7.2.2, 7.3.1).

7.1.6 Cotesting compared to HPV with cytology triage

When cotesting is compared with HPV with cytology triage, HPV with cytology triage was found similarly effective to detect CIN2+ or CIN3+ as cotesting in 6 systematic reviews and meta analyses. One systematic review found the evidence from RCTs too limited to recommend HPV with cytology triage instead of cotesting. One review had other concerns to switch from cotesting to HPV with cytology triage in the primary screening (7.2.2.1.1).

Three of 5 health economic studies showed the same clinical effectiveness for cotesting as for HPV with cytology triage. In these cases the follow up algorithm after cotesting was similar as after HPV with cytology triage. In 2 health economic studies cotesting was more effective than HPV with cytology triage. In 1 of these studies every HPV result was directly followed up with colposcopy and in the other follow up after primary testing was not described (7.3.4).

7.1.7 HPV with genotyping for HPV 16/18

Partial genotyping with HPV 16/18 identifies women with the highest risk for cervical cancer. According to cohort studies the risk to develop CIN3+ in the next 3 years is higher for HPV16/18 positive / cytology negative women than for other hrHPV positive / cytology positive women (7.2.4.1). Therefore a screening strategy with direct referral to colposcopy for HPV16/18 positive women and retesting for other hrHPV positive and cytology negative women was recommended by 3 systematic reviews. One non health economic modelling study came to the conclusion that this strategy had a lower number of cases of cervical cancer with fewer colposcopies (7.2.4.2).
Four health economic studies modelled this strategy. In these genotyping for HPV16/18 always had the highest clinical effectiveness of all strategies. This strategy showed higher colposcopy rates than HPV with cytology triage in 3 of the 4 studies. One study showed a modest absolute increase of colposcopies and the lowest colposcopy rate per detected CIN3+ compared to all other strategies (7.3.1, 7.3.4, 7.3.4.1).

7.1.8 Longer Screening Intervals with HPV vs Cytology

Screening intervals can be prolonged from 3 years with cytology to 5 years with HPV based testing. This was consistently shown by clinical systematic reviews and meta analyses as well as by health economic models (7.2.3, 7.3.3).

7.1.9 Other potential harms and burden from HPV based testing

A systematic review of the results of 3 out of 5 RCTs indicated that the number of positive primary screening test results that were subsequently not associated with CIN3+ (called "false positive" results), was higher with HPV than with cytology testing. The authors assumed this may be compensated over the lifetime of women by longer screening intervals (7.2.4.4). In one health economic study the number of false positive results was modelled. Cytology based screening had higher numbers of false positive results than HPV based screening of the same frequency. The term "false positive" was however not clearly defined in this study (7.3.4.2).

Only limited data are available for psychosocial effects of positive primary screening results with HPV versus cytology. The main difference is that HPV has the connotation of a sexually transmitted disease which may be associated with stigma (7.2.4.5). No data are available on the amount of physical damage from biopsies taken and treatment of precancerous lesions (7.2.4.6).

7.2 Details on Clinical Evidence from Systematic Reviews and Meta Analysis

7.2.1 Protection against cervical cancer

HPV based screening resulted in significantly lower invasive cervical cancer numbers compared with cytology based screening in the combined follow up of 4 European RCTs. A trend towards lower cervical cancer incidence rates is reported in all systematic reviews or meta analyses that discussed this end point.

The endpoint of invasive cervical cancer was addressed by 6 out of 15 systematic reviews or meta analyses.
4 systematic reviews reported “indications” for lower cancer incidence rates in the second screening round and prolonged follow up of the RCTs NTCC and POBASCAM [45, 51, 67, 68].
Quantitative results on the reduction of cervical cancer incidence were reported by IQWIG [46] based on their meta analysis of the results in the second screening round of NTCC, POBASCAM and Swedescreen (RR = 0.24, 95% CI = 0.10-0.60), and by Huh [64] based on the combined follow up of NTCC, POBASCAM, Swedescreen and ARTISTIC of Ronco et al. [39] (RR = 0.45, 95% CI= 0.25–0.81).

The challenge in this end point is that the overall incidence of invasive cervical cancer in an already screened population is low. Therefore, most individual RCTs were not powered to detect a significant reduction in the incidence of cervical cancer cases [39].
Ronco et al [39] analyzed the combined follow up data of women enrolled in the studies ARTISTIC, POBASCAM, Swedescreen and NTCC. Thereby 176’464 women were followed up for a median of 6.5 years.
The results of this combined follow up show that even though differences exist in the detailed algorithms used in the intervention groups (e.g. using cotesting versus HPV testing only as primary screening test and the follow up after a positive HPV results (direct referral to colposcopy versus retesting of HPV+/cyt- women after one year)), there was a common effect of protection against cervical cancer.
Using HPV testing in cervical cancer screening resulted in a significantly lower number of cervical cancers with no significant heterogeneity between studies. The protective effect of HPV testing was more predominant against adenocarcinoma (RR 0.31 (0.14-0.69)), than for squamous-cell carcinoma (RR 0.78 (0.49-1.25)). This is due to the especially low sensitivity of cytology to detect adenocarcinoma. In women with a negative screening test at entry, the rate ratio for all invasive cervical cancer cases was 0.30 (0.15–0.60). From these numbers the authors of this study concluded that HPV based screening provides 60-70% greater protection against invasive cervical cancer compared with cytology [39].

7.2.2 Surrogate markers CIN2+ and CIN3+ over 2 screening rounds

7.2.2.1 Detection of CIN3+ and CIN2+ in round 1

CIN2+ detection was significantly increased in all meta analyses and CIN3+ significantly increased in 3 meta analyses and non-significantly increased in 2 meta analyses in screening round 1 with HPV based testing versus cytology based testing.

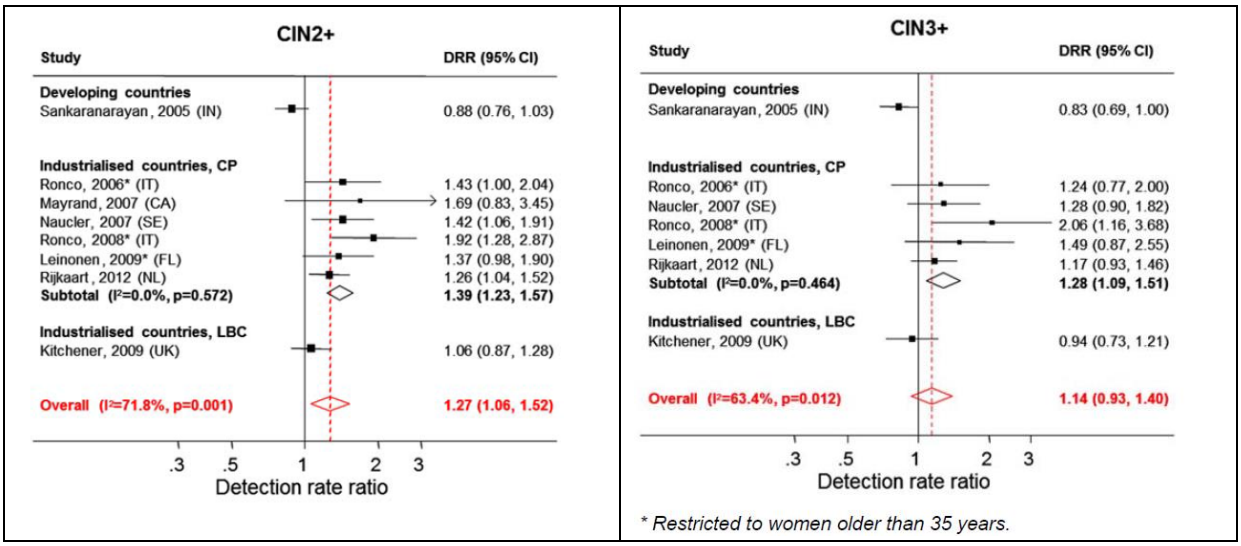
All 9 systematic reviews addressing this surrogate marker [49, 51, 52, 54, 56, 64, 66-68] confirmed that HPV based testing leads to increased detection of CIN2+/CIN3+ without giving quantitative results. These findings were based on the RCTs NTCC, POBASCAM, FPHT, HPV Focal, and ATHENA.
One systematic review [48] did not address this surrogate marker, as its focus was on positive primary test results without subsequent CIN3+ confirmation.

All 5 meta analyses addressing the surrogate markers CIN2+ and/ or CIN3+ came to the same conclusions on the relative detection of CIN2+ and similar conclusions on CIN3+ with HPV based screening versus cytology based screening [43-47].

The quantitative results from the meta analyses are as described in the following paragraphs:

In the most comprehensive meta-analysis from Arbyn [28, 44] (Figure 4), a good overview is given on the results of the RCTs NTCC1 (Ronco [15]), CCCaST (Mayrand [6]), Swedescreen (Naucler [19]), NTCC2 (Ronco [13]), FPHT (Leinonen [8]), POBASCAM (Rejkaart [16]) and ARTISTIC (Kitchener [3]).
HPV based screening algorithms lead to significantly increased detection of CIN2+ and not significantly increased CIN3+ in the first screening round (analysis restricted to women older than 35 years).

Figure 4 Detection of CIN2+ and CIN3+ in the first screening round with HPV testing versus cytology as taken from figures 4 and 5 of [28]



The ARTISTIC study (Kitchener [3]) is shown separately in this meta-analysis because of the high heterogeneity introduced by this study. It was discussed that the comparator used in this study was LBC, newly introduced in the UK with an unusually high proportion of cytology positive samples of up to 17%. The reason that HPV based testing did not detect more CIN2+ or CIN3+ cases might therefore be associated with an unusual high sensitivity threshold of LBC in this study. (It is important to note that in general authors of systematic reviews and meta-analyses did not distinguish between different cytological techniques as comparators to HPV testing and consider Pap test and LBC as equivalent e.g. [52]. In a meta-analysis LBC was found to be neither more sensitive not specific than the Pap test [82]. The main advantage of LBC over the Pap test is that the number of samples of insufficient quality can be reduced.[1]
It was also discussed that in the ARTISTIC study follow up of HPV positive cytology negative women was incomplete. Only 62% of HPV positive women had repeat testing as per protocol and of those persistently positive only 66% underwent colposcopy.
Even with inclusion of the ARTISTIC study the big picture remains that CIN2+ detection was significantly and CIN3+ detection non significantly increased in the first screening round.

The biggest increase in CIN3+ detection by HPV testing was seen in the Italian NTCC1 and 2 studies. These studies differs from others in that it had a comparatively more active follow up of HPV positive cytology negative women. In NTCC1 for women of 35 years and older and in NTCC2 for all women a positive HPV test led immediately to colposcopy while in other studies HPV positive and cytology negative women were invited for retesting after 12-18 months and only women persistently positive for HPV were invited for colposcopy.

The meta analysis by IQWIG [46] showed the same picture. It provided a forest plot of results of the relative detection of CIN3+ at round 1 from NTCC1 and 2, Swedescreen, POBASCAM and ARTISTIC and “FTPH” with pooled results for all age groups (including women younger than 30 years), for CIN3+ detection at round 1. Due to the high heterogeneity across studies it was decided to not calculate a common effect size. However from the graph it is obvious that only the NTCC2 study had a relevant and significant increase in CIN3+ detection in round 1.
The study of CCCaST [6] was not included in this analysis as both intervention and control arms had HPV testing (in different order of sampling).

The meta analysis by Bouchard-Fortier [43] came to the same conclusion that relative detection of CIN2+ is significantly increased and that of CIN3+ not significantly increased even though done across all age groups (including women younger than 30 years). This meta analysis focused on cotesting as intervention and therefore included only NTCC1, ARTISTIC, POBASCAM and Swedescreen.

The meta analysis by Murphy [45] showed a significantly increased detection also of CIN3+ in round 1. It included NTCC 1 and 2 (pooled results over both phases), Swedescreen, POBASCAM and ARTISTIC for CIN2+ results, but excluded ARTISTIC for CIN3+ results due to the high heterogeneity introduced. The analysis included all women including those younger than 30 years.

[1] In Switzerland both methods are used 1. Untiet, S., et al., *[Cervical cancer screening in Switzerland - current practice and future challenges].* Ther Umsch, 2013. **70**(4): p. 223-30.

Both the meta-analyses of Bouchard-Fortier and Murphy did not include FPHT. For this study only results of the first round have been reported and the authors wanted to compare results of the first round with those of the second round and over both screening rounds.

The meta analysis by Pileggi [47] also found a significantly increased CIN3+ detection rate of 1.48 (CI = 1.02-2.13). The difference between this study and the others is that it included the Finnish FPHT study and used results from all women of 25-65 years of age, while Arbyn [44] only used data from women older than 35 years.

In summary: depending on the inclusion or exclusion criteria used, in round 1 CIN2+ detection was always significantly increased, while CIN3+ detection was increased non-significantly or significantly.

7.2.2.1.1 Comparison of HPV testing as primary screening with cotesting in round 1

Testing with HPV alone is similarly effective to detect CIN2+ or CIN3+ than cotesting with HPV and cytology. This was a consistent finding across most systematic reviews and meta analyses that discussed this aspect, while some found the evidence limited.

Only the meta analysis of Arbyn [44] compared in a quantitative manner cotesting with primary testing with HPV alone (with or without triage). The detailed results are shown in Figure 5. They show that no significant difference in the relative detection rate of CIN2+ or CIN3+ was observed in any of the single studies included in the meta-analysis if the numbers of CIN2+ or CIN3+ cases identified by HPV positive samples only were compared to additional cases found in HPV negative, cytology positive women [28, 44].

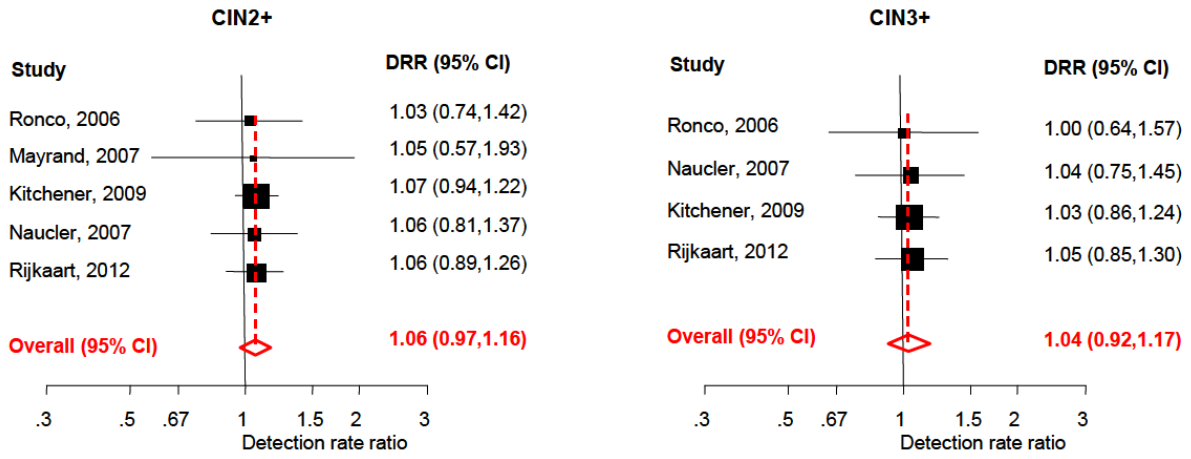
Five systematic reviews [47, 52, 56, 64, 68] stated that HPV testing alone had similar sensitivity for the detection of CIN2+ and CIN3+ as cotesting without stating quantitative results. Evidence was taken from the RCTs included in the meta analysis of Arbyn and the cohort studies KPNC [73], ATHENA [5] and [39, 83]. Whitlock [68] even warned that cotesting might offer no additional CIN3+ detection above HPV screening alone, but may yield more false-positive results.

Moyer [51] found the evidence on benefits and harms of HPV testing alone versus cotesting too limited yet to make a recommendation for it.

Saslow [67] had a concern that with HPV testing alone, problems with sampling of the material for the test might go unnoticed and lead to false negative results, which would be recognized with a cytology sample taken at the same time. No data on the frequency of false negative HPV results were provided by Saslow.

The question was not addressed in the other 7 systematic reviews or meta analyses [43, 46, 48, 49, 52, 54, 66].

Figure 5 Relative detection rate of CIN2+ and CIN3+ with HPV testing alone versus cotesting as taken from figure 6 in [28].



7.2.2.2 Detection of CIN3+ and CIN2+ in round 2

HPV based testing led to significantly fewer CIN3+ stages in the second screening round. This finding was consistent across all meta-analyses. In addition all single studies except NTCC1 showed this result.
Also significantly fewer CIN2+ stages were found in the second screening round. This result is however only based on 2 meta-analyses, and single studies had higher heterogeneity.

For screening round 2 the relative detection of CIN3+ in intervention arm versus control was analyzed in 4 meta analyses [43-46] (Figure 7) and CIN2+ in 2 meta analyses [43, 45] (Figure 6). They were based on the only 4 RCTs containing data for more than one screening round: POBASCAM, NTCC 1 and 2, Swedescreen and ARTISTIC.

Significantly fewer CIN3+ stages were found in the second screening round in the intervention arm versus control. There was no heterogeneity between studies if the age of women was 35 years or older and higher heterogeneity when women of all ages were included. Heterogeneity was highest when NTCC rounds 1 and 2 were separately reported. The background is that in NTCC round 1, in younger women the relative detection rate of CIN3+ was not reduced in round 2, while the reduction in NTCC2 was much more prominent. The difference between NTCC1 and 2 is that in NTCC 1 cotesting was applied and young women positive for HPV but negative for cytology were retested within 12-18 months. The authors commented that only 70% of the women returned for retesting. In contrast in NTCC2 only HPV testing was done and every positive HPV test was followed up with immediate colposcopy.
The same findings were discussed in 3 systematic reviews [51, 56, 68] and were interpreted as a protective effect of HPV based testing in round 1.
Six systematic reviews or meta analyses did not report detection of CIN3+/CIN2+ in screening round 2 [47, 48, 52, 54, 64, 67]

Figure 6 Relative Detection of CIN2+ in the 2nd screening round with HPV versus cytology testing

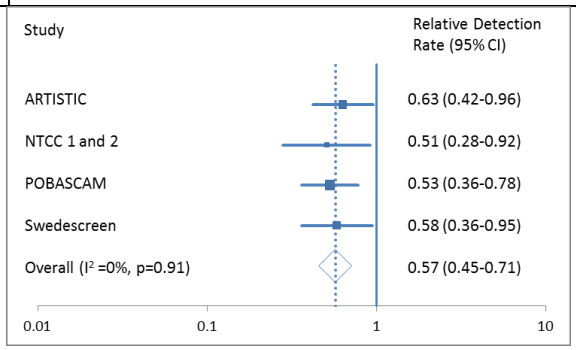
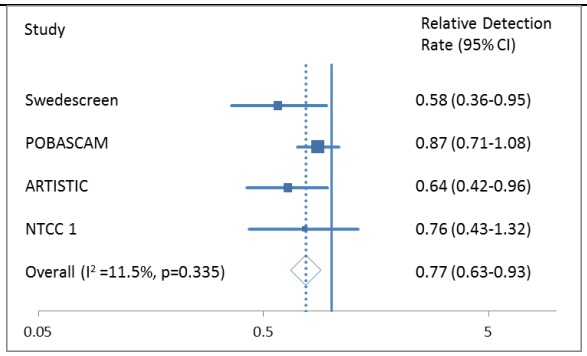
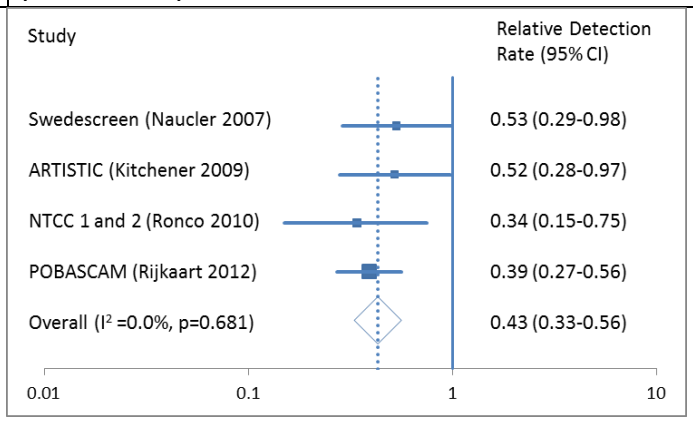
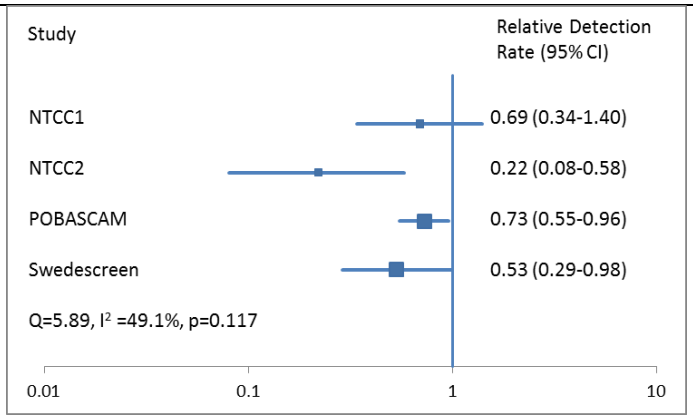
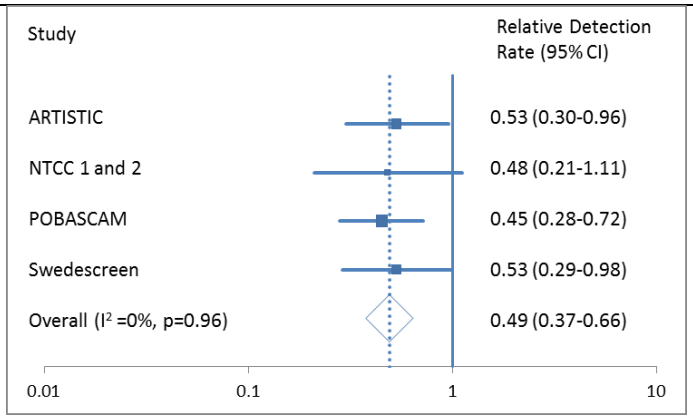
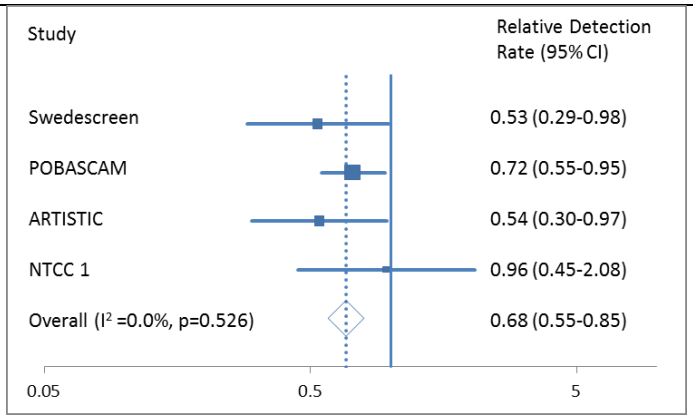
Meta-analysis	Forest Plot (created after Plots in the respective publications)
Murphy [45] All ages Pooled results from NTCC1 and 2 POBASCAM interim results from Bulkmans [17]	
Bouchard-Fortier [43] All ages Only NTCC1, as only cotesting was analyzed as intervention POBASCAM final results based on Rijkaart [16]	

Figure 7 Relative detection rate of CIN3+ in the 2nd screening round with HPV versus cytology testing

Meta-analysis	Forest Plot (created after Plots in the respective publications)
Arbyn [28, 44] women of ≥ 35 pooled results from NTCC1 and 2	
IQWIG [46] All ages ARTISTIC was excluded from analysis of round 2 because more than 30% of the women of round 1 were lost to follow up in round 2. Due to the high heterogeneity no overall value was calculated	
Murphy [45] All ages Pooled results from NTCC1 and 2	
Bouchard-Fortier [43] All ages Only NTCC1, as only cotesting was analyzed as intervention	

7.2.2.3 Detection of CIN3+ and CIN2+ over both screening rounds

Detection of CIN3+ and CIN2+ was similar over 2 screening rounds with HPV versus cytology. This was shown in two meta-analyses. This was true for all individual studies but one (NTCC). This study showed elevated CIN3+ and CIN2+ values over 2 screening rounds indicating that immediate colposcopy after every positive HPV results without triage will lead to overdiagnosis of precancerous lesions while triage with cytology limits overdiagnosis.

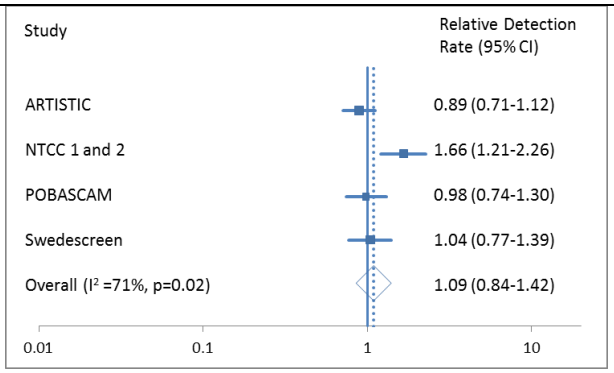
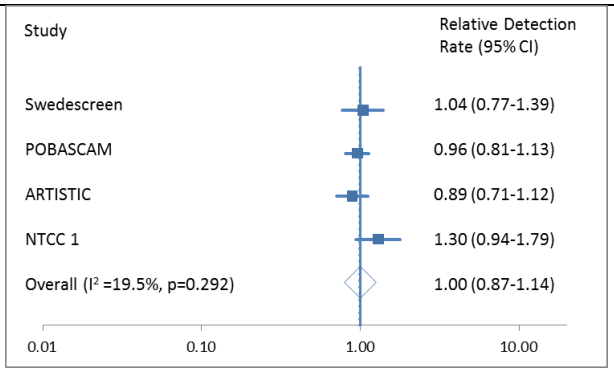
Two publications contained meta analyses on the relative detection of CIN2+ and CIN3+ with HPV based screening versus cytology only screening [43, 45] over two screening rounds (Figure 8).
In these meta analyses the summary measure over all studies showed no significantly changed detection rates of CIN2+ or CIN3+.
One single study showed increased detection of CIN2+ and CIN3+ over both screening rounds, i.e. NTCC2, where every positive HPV result was followed up with immediate colposcopy. CIN2+ was also significantly increased in NTCC1 where women of 30 years and older were followed up with immediate colposcopy and younger women were followed up with retesting after 12-18 months.
The authors of the study concluded that HPV testing in younger women leads to overdiagnosis of CIN2 [12].
At the same time it is important to note that in NTCC1 and 2 also in older women relative cumulative detection rates over 2 screening rounds of CIN2 and CIN3 were significantly increased.
Therefore it may be concluded that immediate referral to colposcopy of every HPV positive woman leads to overdiagnosis of precancerous lesions, a significant number of which would otherwise regress before being detected and treated.

The systematic review of Patanwala [66] interpreted this differently. According to the authors HPV based testing was only more sensitive over 2 screening rounds than cytology based testing if followed by immediate colposcopy.

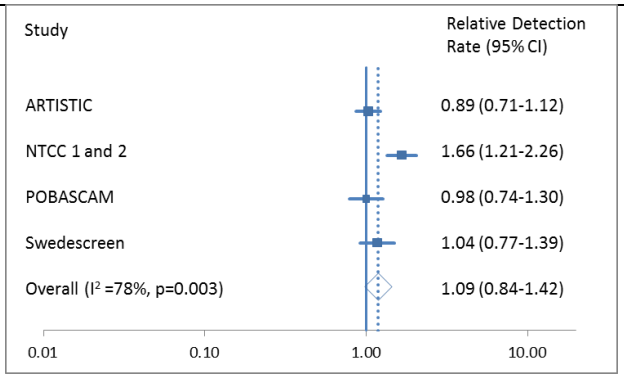
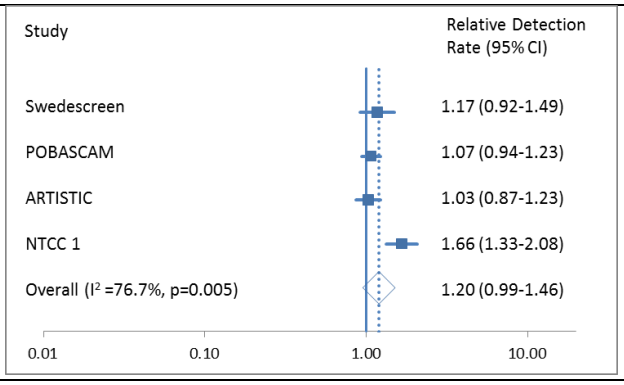
The systematic review of Whitlock [68] also mentioned that cumulative detection rate of CIN3+ over 2 screening rounds was only elevated in NTCC2 (HPV only with direct referral to colposcopy for all ages), but not in NTCC1 (cotesting with direct referral to colposcopy for older women and retesting after 1 year for younger women). The authors were not sure how this result should be interpreted.

The other systematic reviews and meta analyses did not address this indicator.

Figure 8 Relative Detection of CIN2+ and CIN3+ over both screening rounds in the intervention arm vs cytology only

Meta-analysis	Forest Plot (created after Plots in the respective publications)
Murphy [45] All ages Pooled results from NTCC1 and 2	
Bouchard-Fortier [43] All ages Only NTCC1, as only cotesting was of analyzed as intervention	

Relative Detection of CIN2+ over both screening rounds in the intervention arm vs cytology only

Meta-analysis	Forest Plot (created after Plots in the respective publications)
Murphy [45] All ages Pooled results from NTCC1 and 2	
Bouchard-Fortier [43] All ages Only NTCC1, as only cotesting was of analyzed as intervention	

7.2.2.4 Clinical evidence of sensitivity and specificity of cervical screening with HPV tests

HPV tests are 24 to 40% more sensitive but 2 to 8% less specific than cytology tests to detect precancerous lesions CIN2+ or CIN3+.

The absolute sensitivity of the HPV test to detect CIN3+ was most comprehensively shown by Arbyn [28] for the most studied assay HC2 (Hybrid Capture® 2), which was used, e.g. for the RCTs ARTISTIC and NTCC.
In industrialized countries the sensitivity of this HPV assay to detect CIN3+ was consistently high at 0.98 (0.97-0.99). In an earlier meta-analysis the sensitivity of the HPV assay to detect CIN2+ was 0.96 (0.95-0.98) [44]. Arbyn [28] reported that the sensitivity of the HPV assay HC2 to detect CIN3+ was 24% to 40% higher than cytology depending on the disease threshold (CIN2+ or CIN3+), or on the cytological cutoff (ASC-US or Low-grade Squamous Intraepithelial Lesion (LSIL)).

The relative specificity of HC2 for excluding CIN2+ was significantly lower than cytology: ratio of 0.98 (95% CI: 0.96-0.99) and 0.92 (95% CI: 0.90-0.94), considering the cutoffs ASC-US+ or LSIL+, respectively ([28].

Sensitivity and specificity for other HPV tests was also most extensively discussed by Arbyn [28] (Table 4). Of these the most relevant tests are GP5+6+ which was used in the RCTs POBASCAM and Swedescreen and the cobas HPV test which was used in the ATHENA study.
As a summary, these tests showed high inter assay comparability for sensitivity and specificity to detect CIN2+ or CIN3+.

Table 4: Relative accuracy of other HPV tests compared to HC2 to find underlying CIN2+ or CIN3+ in primary screening (taken from table 7 in [32])

Comparison	Outcome	Relative sensitivity (95% CI)	Relative specificity (95% CI)	No. of studies
GP5+6+ / HC2	CIN2+	1.00 (0.96-1.04)	0.99 (0.91-1.07)	2
HPVcare / HC2	CIN2+	0.93 (0.85-1.01)	0.98 (0.96-1.01)	1
Cobas 4800 / HC2	CIN2+	1.00 (0.96-1.04)	0.99 (0.98-1.00)	3
Abbott / HC2	CIN2+	1.00 (0.96-1.03)	1.02 (1.01-1.03)	3
Papillocheck / HC2	CIN2+	0.99 (0.96-1.04)	0.99 (0.98-1.00)	1
BD HPV / HC2	CIN2+	1.00 (0.93-1.07)	0.99 (0.97-1.00)	1
Pretect HPV Proofer / HC2	CIN2+	0.74 (0.61-0.91)	1.12 (1.10-1.13)	1
APTIMA / HC2	CIN2+	0.98 (0.94-1.03)	1.04 (1.01-1.08)	5

7.2.3 Longer Screening Intervals with HPV vs Cytology

A negative HPV test result gives better and longer security against the development of CIN3+ and cancer than a negative cytology result. This was a consistent finding from all systematic reviews or meta analyses addressing this question.

Screening intervals should be chosen based on the probability that disease progresses between intervals to a stage that is beyond the threshold that is considered for treatment. These probabilities are typically developed based on the data observed in cohort studies. The probability after a cytology negative result to develop CIN3+ or cervical cancer over the next 3 years was higher than after a hrHPV negative result over the next 5 years.

This was reported by 7 systematic reviews or meta analyses based on the cohort studies KPNC [11, 72, 73], ATHENA [5] and [39, 83] and in 1 systematic review [68] also based on the RCTs POBASCAM, ARTISTIC, Swedescreen and FPHT.

Longer screening intervals than with cytology without specifying the exact length of the interval were found indicated by Bouchard-Fortier [43] based on the results of the RCTs Swedescreen POBASCAM, ARTISTIC and NTCC. Moyer [51] found evidence from a cohort study in 2007 that instead of 2 yearly cytology testing, 3 yearly cotesting would be possible. According to Moyer the results from ARTISTIC [4] indicate a possible screening interval of even 6 years. Six years was also proposed by Cuzick [49] based on the results from POBASCAM and Swedescreen [17, 19]. Schiffman [52] interpreted the results of cohort studies [83, 84] that a negative HPV results gives 5-10 years of protection against cervical cancer.
Four systematic reviews did not address this question [46-48, 66].

Some results from the above mentioned cohort studies are presented in the following paragraphs:

The biggest cohort study was KPNC in which up to 2011 more than 300’000 women tested with cotesting were followed up for 4-6 years. They showed that the risk to develop CIN3+ in the next 5 years per 100’000 women for HPV negative women was 0.16% when they were also cytology negative, and 0.86% when cytology positive. Cytology negative women who were HPV positive results had a 5.9% risk to develop CIN 3+.

In the ATHENA study 347 cases of CIN3+ were identified over 3 years. 47.3% occurred in baseline cytology negative women and 9.8% in baseline HPV negative women ($p<0.001$) [5].

In the combined follow up of the European RCTs POBASCAM, ARTISTIC, Swedescreen and NTCC, the authors concluded from the cumulative incidence rates of invasive cervical carcinoma that 5 yearly testing with HPV is more protective than 3 yearly cytological testing [39]:
The Cumulative Incidence Rates (CIR) (95% confidence interval) of invasive cervical carcinoma per 100’000 women were significantly lower after 5.5 years with a HPV negative result than after 3.5 years with a cytology negative result.

	After 3.5 years	After 5.5 years
I=HPV negative women	4.6 (1.1-12.1)	8.7 (3.3-18.6)
C=cytology negative women	15.4 (7.9-27.0)	36.0 (23.2-53.5)

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7.2.4 Quantitative results on the burden of HPV based screening

Direct referral to colposcopy after an HPV result leads to highly increased colposcopy rates, while HPV testing with cytology triage does not (shown from data of RCTs). Based on models 5 yearly HPV based screening with cytology triage will lead to fewer colposcopies / 1000 women than 3 yearly cytology based screening. In addition partial genotyping for HPV 16/18 to triage women for immediate colposcopy was recommended based on data from cohort studies.
The number of positive primary screening test results per screening round is higher with HPV than with cytology testing. This may be compensated over the lifetime of women by longer screening intervals.
Only limited data are available for psychosocial effects of positive primary screening results with HPV versus cytology. No data are available on the inconvenience of more frequent testing, or the amount of physical damage from biopsies taken and treatment of precancerous lesions.

7.2.4.1 Colposcopy Rates from RCTs and cohort studies

Several systematic reviews and meta analyses stated that RCTs were deficient in the reporting of follow up events such as colposcopies, biopsies, treatments and adverse events [43, 44, 46, 65, 67, 68]. Some analysis was possible however to estimate the burden of screening with HPV compared to cytology:

In NTCC with direct referral to colposcopy after every positive HPV result 3 systematic reviews [45, 66, 68] reported that colposcopy rates were much higher in the intervention than in the control group.
Schiffman [52] judged that based on the data from the KPNC cohort direct referral to colposcopy would double the colposcopy rate from current practice. (Current practice in the US with 5 yearly cotesting refers HPV positive / cytology negative women to retesting after one year). Massad [54] argued that based on KPNC, direct referral to colposcopy for these women is not necessary as the risk to develop CIN3+ over 5 years is lower than 5%. Therefore Massad agrees that retesting of HPV positive/ cytology negative women after one year is indicated.

In RCTs where HPV positive women were followed up with cytology triage and retesting after 1 year if cytology negative, a less consistent picture emerged:
Whitlock [68] reported that in the Finnish trial FPHT, where HPV testing with cytology triage was applied, colposcopy referrals were not elevated (0.9% vs 1.0% in the control group). However Whitlock criticized that only initial colposcopy rates were reported and may not show the full picture. Whitlock found that in POBASCAM [17] and ARTISTIC [3] the reported cumulative colposcopy rates were slightly higher in the cotesting group than in the cytology group (3.4% vs 2.8% in POBASCAM and 6.0% vs 4.9% in ARTISTC).

Patanwala [66] tried to calculate colposcopy rates in round 1 per CIN3+ case detected for all studies and found that rates were significantly elevated in ARTISTIC (5.4 colposcopies in the intervention arm, 4 in the control arm $p<0.01$), while in the other studies rates were not significantly higher in the intervention group.

Numbers of biopsies taken in RCTs were analyzed only in the study of Ronco [39], which followed up all women participating in the RCTs NTCC, ARTISTIC, Swedescreen and POBASCAM. Ronco et al. were able to retrieve the number of women who had biopsy over the entire period of observation. They found that in ARTISTIC, Swedescreen and POBASCAM where HPV testing was followed by cytology triage, biopsy rate ratios in the intervention and control groups were comparable (pooled rate ratio 1.02 (0.97-1.07) with no heterogeneity). However in NTCC, where women of 35 years and older (NTCC1) or even women of all ages (NTCC2), were transferred to colposcopy after a single HPV positive test, the relative rate of women with biopsies was increased twofold in the intervention arm versus the control arm.

A partial genotyping strategy where HPV 16/18 positive women are followed up with immediate colposcopy was indicated based on cohort study results from KPNC, VUSAscreen and ATHENA. They show that the risk of developing CIN3+ over the next 3 years is higher for HPV16/18 positive/ cytology negative women than for those positive for other hrHPV types and positive for cytology.
Based on cohort studies 3 systematic reviews [54, 56, 64] recommend the strategy of partial genotyping with direct colposcopy for HPV16/18 positive results and retesting after one year for women positive for other HPV strains and cytology negative.

7.2.4.2 Colposcopy Rates from modelling

Several systematic reviews came to the conclusion that the calculation of benefits and harms (in terms of colposcopy rates), can only be done by modelling.
Colposcopy rates in the first screening round were typically higher in the intervention arm, in line with increased detection of precancerous stages [45]. What is of interest for a screening strategy for a health system and for the affected women, is the overall number of colposcopies done during the life time of each woman. As HPV based screening allows longer screening intervals, increased rate of colposcopies per screening round can be counterbalanced by reduction of number of screening rounds.
Modelling studies were referred to by 4 systematic reviews [51, 56, 67, 85].

Saslow [67] Moyer [51] (and ACOG by making reference to Saslow), make reference to a modelling study of Kulasingam [86] in the context of clinical guidance development for the US health system. This modelling study comes to the conclusion that the number of colposcopies per 1000 women will be lower with HPV based screening algorithms with a 5 year screening interval than with a cytology only based screening interval every 3 years. The same result was achieved using test performance data from three different studies [6, 87, 88].

Huh [64] makes reference to a modelling study done based on the data from the industry sponsored ATHENA cohort study. In this modelling study it was expected that the number of colposcopies per CIN3+ case detected would be lower with HPV testing with partial genotyping for HPV16/18 than with cytology [89].
The US-FDA came to the conclusion that partial genotyping for HPV 16/18 with direct referral to colposcopy and cytology triage for other hrHPV types detected more disease cases when compared with cytology based screening, with fewer colposcopies and approximately the same number of screening tests

7.2.4.3 Recommended HPV based strategies based on RCTs, cohort studies and non-health economic modelling

In order to minimize the number of unnecessary colposcopies a number of recommendations were made in the systematic reviews or meta analyses. These are presented in the following paragraphs:

Colposcopy after every HPV positive result is not recommended by any of the systematic reviews or meta analyses.

Five yearly HPV testing with cytology triage is recommended by 3 systematic reviews based on modelling studies [51, 56, 67]. In this strategy colposcopy is only indicated if HPV positive women are also cytology positive. If women are HPV positive /cytology negative retesting after one year is recommended.

Partial genotyping for HPV16/18 and referral to colposcopy if positive was recommended by 3 systematic reviews [54, 56, 64].

Patanwala [66] did not make a recommendation on triage and colposcopy strategies. In contrast to the other systematic reviews or meta analyses, they interpreted that only in NTCC with direct referral to colposcopy after an HPV result, was the sensitivity of HPV testing higher than with cytology testing over 2 screening rounds. This was based on the fact that with other strategies the cumulative CIN3+ incidence rates of 2 screening rounds was not increased [66] (as discussed in chapter 7.2.2).

The German study by IQWIG [46, 65] also did not make any recommendation on HPV based testing as they found the evidence for potential harms insufficient and the ideal strategy to follow up on positive HPV results unclear based on the RCT results. The authors questioned whether the results of the RCTs would be transferable to the German context as treatment recommendations in Germany are different from the practice applied in the RCTs.

7.2.4.4 Number of positive primary screening test results

The systematic review of Rebolj [48] focused on the lower specificity of the HPV test compared to cytology and analyzed how many women will be diagnosed with a false positive screening result from their primary cervical screening test, if this test is HPV versus cytology. A “false positive” screening result in this study is defined as the result of any primary screening test that leads to either retesting, triage testing of a secondary screening test or colposcopy and/ or biopsies, but is not associated with CIN3+. With the definition used in this study the frequency of false positive tests was increased with HPV testing in women above 30 years in the studies POBASCAM, Swedescreen and NTCC by a factor or 2 to 4, whereas it was not increased in ARTISTIC and lower in FPHT. Rebolj proposed that the latter was a result of the lower specificity of cytology testing in ARTISTIC and FPTH due to lower cut off values. Rebolj recommended counterbalancing the total number of false positive results in a woman’s lifetime by applying longer screening intervals.

7.2.4.5 Psychosocial Aspects

Three systematic reviews make reference to studies targeted specifically at the reaction to a positive HPV result [49, 56, 68]. Different to a cytological test result, a HPV infection has the connotation of a sexually transmitted disease and may involve stigma leading to insecurity in sexual behaviors and questions about relationships. Cuzick mentioned that women from

particular ethnic and religious backgrounds express fears that community leaders could be less supportive of cervical screening if they were aware of the link with sexual transmission [49]. Whitlock made reference to a study on 4104 women in the UK and Australia that showed increased levels of immediate anxiety and distress in women who tested positive for HPV compared with those who tested negative. This difference was resolved by 6 months follow up [68].
No data were shown whether the amount of distress is different after a positive HPV result than after a positive cytology result.

The other systematic reviews and meta analysis either did not address psychosocial aspects or found that available data from RCTs were insufficient.

Inconvenience of more frequent testing or the absolute number of screening tests / women were not addressed in the systematic reviews or meta analyses.

7.2.4.6 Physical damage from biopsies or treatment of precancerous lesions

No data were reported on this topic in any of the meta analyses or systematic reviews. In general reporting from RCTs on potential downstream issues of follow up diagnostic tests and treatment were found to be insufficient.

7.3 Details from HTAs and health economic studies

All extracted details from HTAs and health economic studies are shown in the Appendix in Table 10. Results from HTAs and health economic studies relevant for clinical effectiveness and the burden of screening are compiled in Table 5. The relevant information from these tables will be discussed in the following chapters.

Thirteen health economic publications had sufficient detail of result reporting and had a comparator of at least 3 yearly cytology testing and so were included in the quantitative analysis for research questions 1a, b and c [2, 28-30, 32-37, 60, 75, 76]. One publication is an English publication of the central results from a German HTA. The 2 publications are henceforth referred to as 1 study [30, 60].

Eleven of 12 studies modelled the natural history of cervical cancer from HPV infection over the development of precancerous lesions to cervical cancer and successful treatment or death. Models were typically calibrated to reflect HPV prevalence and cancer incidence in the country the study was done for. The health economic study in the HTA from Belgium [28] used a different approach by directly simulating patterns of detection of precancerous lesions and cancer according to results of a meta analysis done from the European RCTs [28, 44] in a hypothetical cohort screened with 3 yearly cytology testing and another cohort screened with 5 yearly HPV based testing [80].

Modelled screening strategies include cytology only, cytology with HPV triage, HPV with direct referral to colposcopy, HPV with cytology triage, HPV with partial genotyping for HPV16/18 and cotesting. Different screening frequencies for the primary screening rounds and different frequencies for retesting after HPV+/cyt- results were also modelled.

7.3.1 Protection against cervical cancer, life years gained and QALYs

In all 12 studies HPV based screening strategies were more effective than cytology based screening. HPV with cytology triage was the most studied strategy. In 4 studies HPV based screening with partial genotyping for HPV16/18 was analyzed and found even more effective. Results on cotesting and on HPV with direct referral to colposcopy are less consistent between studies.

Summary effects were typically measured in LYG or QALYs. Effects were discounted with discount rates between 1.5% and 5%. Only one study did not discount effects [36]. As effects in discounted life years or QALYs are small and not intuitive to understand, and undiscounted life years or QALYs were typically not shown, in addition effects in more illustrative measures such as % reduction in cancer risk or reduction in cancer incidence rates are shown in the summary from health economic studies in Table 5, if they were available.

In all 12 health economic analyses, HPV based screening strategies were more effective than cytology based screening as measured in LYG, QALYs, reduction of cancer incidence rates, reduction of life time cancer risk and number of cancer cases (depending on which effect measures were reported).

The most often studied strategy was HPV with cytology triage. Other investigated strategies were cotesting, HPV testing with direct referral to colposcopy and HPV testing with partial genotyping for HPV16/18.

Quantitative results of **cotesting compared to HPV based testing alone or with HPV with cytology triage** were shown in 5 studies [29, 30, 33, 36, 37, 60]. In 2 additional studies cotesting was modelled, but dominated in the economic analysis and no detailed numbers on effectiveness markers provided [2, 35].
Three of the 5 studies showed the same clinical effectiveness for cotesting as for HPV with cytology triage [29, 30, 33, 60]. In these cases the follow up algorithm after HPV and cytology results was similar to that after HPV with cytology triage.
In the other 2 studies cotesting was more effective [36, 37]. In one of these two, positive results of either HPV or cytology were followed up directly with colposcopy. In the other one HPV positive/ cytology negative women were followed up with retesting [36].

One study compared only cotesting with cytology based screening. In this study 3 cotesting screening events in a woman's lifetime at the age of 32, 41 and 50 were more effective than 3 yearly cytology at the age 32-50 years followed by 5 yearly cytology until the age of 60 [75].

"**HPV testing only"** was modelled in 3 studies. No clear picture emerges from these three studies. In one study HPV positive women were directly referred to colposcopy, which was more effective than HPV with cytology triage [33]. In one study follow up after positive results was not clearly described. In this study "HPV only" yielded slightly lower QALY numbers than HPV with cytology triage and the same reduction of cancer risk with 3 yearly screening and slightly higher reduction of cancer risk with 5 yearly screening [76]. In the 3rd study the strategy named "HPV only" was in fact rather a "HPV with cytology triage" strategy as 70% of the women with positive HPV results received cytology or cotesting as triage and only 23% were directly referred to colposcopy (according to the description of the strategy). In this study not surprisingly "HPV only" had similar effectiveness as HPV with cytology triage [30].

HPV with genotyping for HPV16/18 was modelled in 4 studies and was always the most effective strategy regardless of whether it was measured in LYG, QALYs or cancer incidence rates [2, 29, 36, 37]. This strategy showed higher colposcopy rates in 3 of the 4 studies and a modest increase in 1 study [37]. The latter study calculated that the number of colposcopies per detected CIN3+ was lowest with HPV16/18 genotyping compared to all other strategies.

For transparency on excluded studies it should be noted that of the 5 studies that were excluded from this quantitative analysis because they either lacked detailed enough result reporting or only 5 yearly cytology as comparator, all but one also showed that HPV based testing was more effective than cytology based testing. In one study results were only shown in a graphical representation and HPV based screening yielded fewer QALYs than cytology based screening. No detailed analysis of this result was possible and the result was not discussed in the publication [78].
Another excluded study (de Kok [80]) aimed at simulating screening scenarios for different countries with varying background risks for cervical cancer and HPV prevalence. In this

model, HPV based testing was also more clinically effective than cytology based screening if applied at the same or lower frequencies. However only results for certain cost effective strategies are shown in the publication. 3 yearly cytology based screening was not among the strategies that were cost effective under the assumed Swiss scenario conditions, therefore no quantitative clinical and cost results were reported for this strategy. A general description of the study and results are included in Table 10.

7.3.2 Surrogate Markers CIN2+ and CIN3+

The detection rate of surrogate markers CIN2+ or CIN3+ were typically not reported in the health economic models.

7.3.3 Longer Screening Intervals with HPV vs Cytology

Screening intervals can be increased from 3 yearly to 5 yearly screening when switching from cytology to HPV based screening based on the results of all 6 studies that compared these frequencies with slightly higher numbers for LYG, QALYs and lower numbers for cancer incidence rates, cancer case numbers or life time cancer risk.

Five yearly HPV testing was more effective than 3 yearly cytology based testing in all 6 studies that addressed this question [28, 30, 32, 34, 35, 60, 76], and more effective than 2 yearly cytology based testing in 1 additional study [29].
Three yearly HPV testing was more effective than 3 yearly cytology based testing in 2 studies [29, 33] and more effective than 2 yearly cytology based testing in 1 study [36].
Six yearly HPV testing was modelled in 2 studies and was found more effective than current cytology based screening with 3 yearly frequencies up to 49 years followed by 5 yearly screening in one study [2] and less effective than 3 yearly cytology based screening in the other study [32].
One study found that 3 cotesting screening events in a woman's lifetime were more effective than 3 yearly cytology based testing from age 32-50 and 5 yearly cytology between 50 and 60 years [75].

The differences between 5 yearly HPV based screening versus 3 yearly cytology based screening measured as reduction of cancer risk ranged from 0.2% -11%. Bigger differences were reported, when the same screening frequency was compared between strategies.

7.3.4 Potential burden of HPV based Cervical Cancer screening

7.3.4.1 Number of colposcopies

Only 4 studies reported quantitative results for numbers of colposcopies. Strategies with higher clinical effectiveness typically also had higher colposcopy rates. HPV with cytology triage led to similar or modestly increased colposcopy rates (consistent from all 4 studies), while HPV16/18 genotyping showed higher colposcopy rates in 3 of the 4 studies and modest increase in 1 study. The latter study calculated that the number of colposcopies per detected CIN3+ was lowest with HPV16/18 genotyping compared to all other strategies. HPV with direct referral to colposcopy showed very high colposcopy rates (1 study).

The potential burden of screening was addressed in 4 studies by reporting colposcopy numbers [2, 29, 33, 37].

MSAC showed that HPV with cytology triage had slightly elevated colposcopy rates compared to cytology with HPV triage (4-7%) accompanied with higher clinical effectiveness. Cotesting had higher colposcopy rates than HPV with cytology triage with the same clinical effectiveness in terms of cancer incidence rates. HPV 16/18 genotyping resulted in even higher colposcopy rates (21-24%), however with higher clinical effectiveness in terms of cancer incidence rates and life years [29].

Kitchener showed that 6 yearly HPV with cytology triage had similar colposcopy rates as LBC with HPV triage (3 yearly from 25-49 years, then 5 yearly) (-4% up to +10% depending on details in the follow up). 6 yearly genotyping for HPV16/18 resulted in higher colposcopy rates (26-50%) with the highest clinical effectiveness [2].

Vijayaraghavan showed colposcopy rates for cytology only strategies between 170-700/100'000 women, 3 yearly HPV with cytology triage or cotesting had slightly higher rates of 830 and 3 yearly HPV only with direct referral to colposcopy much higher rates of 2000/100'000 women [33]. 5 yearly HPV with cytology triage was not modelled.

Huh showed that 3 yearly HPV with cytology triage had slightly higher colposcopy rates than 3 yearly cytology with HPV triage 2'339 versus 2'104/100'000 women/year. HPV16/18 genotyping in this study had colposcopy rates between cytology with HPV triage and HPV with cytology triage (2'159). Cotesting had the highest colposcopy rates (2'967).
In this study colposcopies / CIN3+ were calculated and were lowest for HPV 16/18 genotyping (3.06) followed by HPV with cytology triage (3.95), cytology with HPV triage (4.76) and cotesting (4.79) [37]. No 5 yearly strategies were modelled; therefore no comparison of colposcopy rates of 5 yearly HPV based screening with 3 yearly cytology with HPV triage is available.

7.3.4.2 Number of false positive results

One study modelled the number of false positive results [34]. Unfortunately there is no clear definition of "false positive" in the publication. It is assumed for this thesis that a false positive result is a screening result that will lead to further observation, however upon follow up will not be associated with precancerous lesions.
In this study 3 yearly and 5 yearly HPV with Pap triage had much lower numbers of false positive test results than 3 yearly Pap testing (5'585 and 2'871 versus 20'529). 2 yearly cotesting had the highest false positive result numbers (82'340).

7.3.4.3 Use of QALYs

QALYs are used in cost utility studies to differentiate between the value of a year of life in perfect health and a year of life with different degrees of illness. Life years are thereby adjusted by different factors ("utilities") depending on the degree of physical, emotional or mental impairment associated with the disease and / or intervention under investigation. Therefore the use of QALYs has the potential to reflect the burden of screening if utilities are calculated for all aspects of screening that may reduce the quality of life of the participating women.

In total QALYs were used by 6 studies. The applied sets of utilities varied between the studies and QALYs typically did not reflect all possible disutilities associated with screening strategies [29, 33, 35-37, 76].

Two studies of the 6 associated disutilities (utility factors of less than 1) only with cancer [35, 76].
Three assigned disutilities to precancerous lesions. In these studies HPV based screening strategies were still more effective than cytology based screening strategies [33, 36, 37].

Only one study associated disutilities with the experience of being screened regardless of the results. This was based on a recent study in Australia which was specifically designed to obtain weights relevant to cervical screening and HPV vaccination in an age-representative sample of women invited for screening. This set of QALYs was also the only one which associated disutilities with colposcopies. Using these utilities HPV based screening with genotyping and HPV based screening without genotyping had the same effectiveness [29], while measured in life years, HPV based screening with genotyping had been more effective. This is likely due to the higher colposcopy rate associated with this strategy.

The other studies refrained from using QALYs due to the perceived limited evidence around utility generation or because specific utility sets were missing for the country the study was concerned with.

Table 5: Comparison of the clinical effectiveness and burden of the most important screening strategies modelled in HTAs and health economic studies

Study, Country	Cytology based testing	HPV only or HPV with cytology triage	HPV testing with HPV16/18 genotyping	Cotesting
MSAC 2014 Australia [29]	All cytology based screening strategies were less effective than all HPV based strategies	5 yearly HPV with cytology triage is more effective in reducing cancer incidence than cytology only or cytology with HPV triage at higher frequency at 25-49 years with modestly higher colposcopy rates	5 yearly HPV with HPV 16/18 genotyping yielded the best result in terms of LYG and cancer incidence rate, however with higher colposcopy rates	Cotesting 5y has the same effect as HPV with cytology triage but with higher colposcopy rates
	Current practice in Australia is 2-yearly Pap test with Pap retest. The closest comparator to Swiss screening is cytology with HPV triage with 3 yearly testing from 25 to 49 and 5-yearly testing from 50-65 and an exit test at age 69 (“IARC” frequencies). Strategies — cancer incidence ASR/100’000 — discounted life years 1. Current practice 2y — 6.9 — not shown 2. Cytology only IARC — 7.6 — 21.62678 3. Pap +HPV triage IARC — 6.2 — 21.6276 4. LBC + HPV triage IARC — 6.1 — 21.62764 5. HPV + cyt triage 5y — 5.8 — 21.62779 6. HPV16/18 genotyping 5y — 5.7 — 21.62792 7. Cotesting 5y — 5.8 — 21.62783		If QALYs were compared, with “QALY set 1” HPV with genotyping has similar effectiveness as HPV without genotyping. This QALY weight set used a new set of weights from a study conducted in metropolitan Sydney, which was specifically designed to obtain weights relevant to cervical screening and HPV vaccination in an age-representative sample of women invited for screening. This set of weights assigned some disutility to the experience of being screened, even if the test result was negative. Burden of screening as measured in colposcopies: Strategies — number of colposcopies 1. Current practice 2y — reference 2. Cytology only IARC — -12% 3. Pap +HPV triage IARC — +13% 4. LBC + HPV triage IARC — +16% 5. HPV + cyt triage 5y — +20% 6. HPV16/18 genotyping 5y — +37% 7. Cotesting 5y — +33%	

<table>
<tr><th>Study, Country</th><th>Cytology based testing</th><th>HPV only or HPV with cytology triage</th><th>HPV testing with HPV16/18 genotyping</th><th>Cotesting</th></tr>
<tr><td>Kitchener et al. 2014
UK [2]</td><td>LBC with HPV triage was less effective than any HPV based strategy</td><td>6 yearly HPV with LBC triage was more effective than cytology based testing at moderately higher colposcopy rates</td><td>6-yearly HPV based testing with HPV 16/18 genotyping was more effective than strategies without genotyping, however at higher colposcopy rates</td><td>No results are shown for cotesting as it was dominated in the cost effectiveness analysis</td></tr>
<tr><td></td><td colspan="4">The burden of screening was addressed by showing colposcopy rates. Strategies with HPV with LBC triage had lower or slightly elevated colposcopy rates compared to current practice., whereas strategies with HPV16/18 genotyping elevated colposcopy rates by 26 to 50%.

Strategy coded as follows: Strategy Code, months follow up after negative triage test, age of switch from cytology to HPV based strategy if strategy was not applied from 25 years on. (CP) current practice =, 3-yearly from 25-49 years, then 5-yearly. All HPV based strategies shown had a frequency of 6 yearly

<table>
<tr><th>strategy code</th><th></th><th>Life years</th><th>Increase of colposcopies vs CP</th></tr>
<tr><td>• CP</td><td>LBC with HPV triage</td><td>26.2307</td><td></td></tr>
<tr><td>• S1 24m 30y</td><td>HPV with LBC triage</td><td>26.2308</td><td>1%</td></tr>
<tr><td>• S2 24m</td><td>HPV with LBC triage (immediate) and HPV 16/18 genotyping (after 24 months) for women who were HPV pos/ cyt neg</td><td>26.231</td><td>-4%</td></tr>
<tr><td>• S2 24m 30y</td><td>HPV with LBC triage (immediate) and HPV 16/18 genotyping (after 24 months) for women who were HPV pos/ cyt neg</td><td>26.231</td><td>10%</td></tr>
<tr><td>• S3 24m</td><td>HPV with HPV 16/18 genotyping</td><td>26.2316</td><td>26%</td></tr>
<tr><td>• S1 12m</td><td>HPV with LBC triage</td><td>26.2317</td><td>10%</td></tr>
<tr><td>• S2 12m</td><td>HPV with LBC triage (immediate) and HPV 16/18 genotyping (after 24 months) for women who were HPV pos/ cyt neg</td><td>26.232</td><td>26%</td></tr>
<tr><td>• S3 12m</td><td>HPV with HPV 16/18 genotyping</td><td>26.2323</td><td>50%</td></tr>
</table>
</td></tr>
</table>

Study, Country	Cytology based testing	HPV only or HPV with cytology triage	HPV testing with HPV16/18 genotyping	Cotesting
Huh, 2015, USA [37]	Cytology with HPV triage was less effective than HPV based testing	HPV with cytology triage was effective than cytology based testing	HPV16/18 genotyping was more effective than cytology triage and resulted in the lowest colposcopy rate / CIN3+ detected	Cotesting was less effective than HPV16/18 genotyping with higher colposcopy rates
	3 yearly HPV testing with HPV16/18 genotyping yielded the most Life-years (LY), the most QALYs and the lowest mortality (not shown). Strategy (3 yearly) LY QALY Colposcopies/ 100'000 women / year colposcopies /CIN3+ • cytology + HPV triage = 37.978 22.856 2.104 4.76 • HPV + cytology triage = 37.981 22.866 2.339 3.95 • cotesting = 37.982 22.868 2.967 4.79 • HPV + 16/18 genotyping = 37.984 22.874 2.159 3.06 Burden of screening: HPV testing with genotyping increased colposcopies only slightly compared to cytology with HPV triage and less than HPV testing with cytology triage and cotesting. HPV testing with genotyping had the lowest number of colposcopies per CIN3+. QALYs: Disutilities were assigned to CIN1,2,3 and cervical cancer, however not to screening itself, or being in triage after an initial positive screening test			
Vijayara-ghavan et al. 2010 USA [36]	2 yearly cytology based screening was less effective than any 3 yearly HPV based screening strategy	3 yearly HPV with cytology triage was more effective than 2-yearly cytology	HPV with 16/18 genotyping and cotesting with 16/18 genotyping was more effective than HPV with LBC triage	3 yearly cotesting with HPV 16/18 genotyping was the most effective strategy
	Strategies cancer incidence QALYs • LBC (2y) 9.17 28.6623 • LBC with HPV triage (2y) 8.56 28.6651 • HPV with LBC triage (3y) 7.86 28.6670 • co- testing (3y) 7.49 28.6714 • HPV with genotyping (3y) 7.57 28.6725 • co- testing. + genotyping (3y) 6.62 28.6745		The burden of screening was only addressed by using QALYs. Disutilities were assigned to CIN and cancer not to being screened per se or to being in triage after positive test result.	

In the following studies no genotyping strategy was included

Study, Country	Cytology based testing	HPV only or HPV with cytology triage	Cotesting
Sroczynski et al. 2010, 2011 Germany [30, 60]	3 yearly cytology was less effective than any HPV based strategy Life Years: 28.869 % reduction cancer risk: 70%	3 yearly HPV based testing had higher effectiveness than 3 yearly cytology 5-yearly HPV based testing had similar effectiveness than 3 yearly cytology 3 yearly: Life Years 28.875, % reduction cancer risk 85% 5 yearly: Life Years Not shown, % reduction cancer risk 72%	Same effect as HPV with Pap triage
	The burden of screening was not modelled (no numbers of colposcopies were calculated, no QALYs were used).		
Arbyn et al. 2015 Belgium [28]	3 yearly cytology with HPV triage was less effective than 5 yearly HPV with cytology triage Life Years: 3'658'751 # of cancer cases: 462	5-yearly HPV testing was more effective than 3 yearly cytology 5 yearly HPV with cytology triage: Life Years 3'660'369, # of cancer cases 222	Not assessed
	The burden of screening was not modelled (no numbers of colposcopies were calculated, no QALYs were used).		
Accetta et al. 2010 Italy [76]	3 yearly Pap testing with HPV triage was less effective than HPV based testing 3y Pap: QALYs 29.42822, % reduction cancer risk 52.9 3y Pap with HPV triage: QALYs 29.42803, % reduction cancer risk 49.5	Compared to Pap test only or to 3-yearly Pap test with HPV triage, 3 yearly or 5 yearly HPV with Pap triage was more effective in reducing life time risk of cancer. 3-yearly HPV test only reduced the risk of cancer to the same level but yielded fewer QALYs than HPV with Pap triage. 3y HPV/PAP triage: QALYs 29.43048, % reduction cancer risk 56.0 3y HPV only: QALYs 29.43042, % reduction cancer risk 56.0 5y HPV/PAP triage: QALYs 29.42991, % reduction cancer risk 55.0 5y HPV only: QALYs 29.42958, % reduction cancer risk 53.7	Not assessed
	The burden of screening was partially addressed by using QALYs. However, no disutilities were assigned to screening itself, colposcopies, being in triage or being treated for CIN.		

<table>
<tr><th>Study, Country</th><th>Cytology based testing</th><th>HPV only or HPV with cytology triage</th><th>Cotesting</th></tr>
<tr><td>Burger et al. 2012 Norway [32]</td><td>3 yearly cytology testing with cotesting triage was less effective than 5 yearly HPV based testing

Life Years / % reduction of cancer
3 y Cytology with cotesting triage: 32.9502 / 55.45</td><td>3, 4, or 5 yearly HPV with cotesting triage was more effective than 3 yearly cytology
6-yearly HPV with cotesting triage was less effective than 3 yearly cytology

Strategies coded by yearly frequency, Primary screening test, months to rescreen triage negative women, colposcopy after three HPV+/cyt- results if not otherwise mentioned
Strategy (all with cotesting triage) / Life Years / % reduction of cancer
HPV 6y, 12m: 32.9500 / 55.59
HPV 5y, 12m: 32.9510 / 58.82
HPV 4y, 12m: 32.9524 / 63.44
HPV 4y, 6m: 32.9529 / 65.26
HPV 3y, 6m: 32.9542 / 70.22
HPV 3y, 6m, colposcopy after 1 repeated HPV+/cyt-: 32.9543 / 70.49</td><td>Not assessed</td></tr>
<tr><td colspan="4">The burden of screening was not modelled (no numbers of colposcopies were calculated, no QALYs were used). Some burden (women’s time and productivity loss was translated into cost and has influenced the cost effectiveness of strategies (see cost effectiveness results)</td></tr>
<tr><td>Goldhaber-Fiebert et al. 2008 USA [35]</td><td>3 yearly cytology based testing was less effective than 5 yearly HPV based testing

QALYs / % reduction of cancer risk
3 y Cytology with HPV triage: 26.72766 / 61.5%</td><td>5 yearly HPV with cytology triage is slightly more effective than 3 yearly cytology with HPV triage
3 yearly HPV with cytology triage is much more effective
Strategies are coded as follows:
Start age with cytology, switch age, strategy after switch, frequency in years,
Strategy / % reduction cancer risk / QALYs
25, 35, HPV with cyt triage, 5y: 61.6% / 26.72609
25, 30, HPV with cyt triage, 5y: 62.3% / 26.72733
25, 35, HPV with cyt triage, 3y: 70.7% / 26.73237
25, 30, HPV with cyt triage, 3y: 71.5% / 26.73344</td><td>As this strategy was either dominated in the cost effectiveness analysis or at an ICER <3Mio$/QALY no data were shown</td></tr>
<tr><td colspan="4">The burden of screening was not directly addressed apart from time and travel cost of women for screening, diagnostic follow up and treatment. No numbers of colposcopies were compared between studies. QALYs had no disutilities assigned to screening, being in triage or being treated for CIN2/3.</td></tr>
</table>

<table>
<tr><td rowspan="2">Vijayara-ghavan et al. 2010 Canada [33]</td><td>3 yearly cytology with HPV triage was less effective than HPV based strategies

Screening Strategy | Annual Cancer Incidence | QALY
No screening | 1’282 | 17.7817
Cytology only 3y | 339 | 17.8196
Cytology+HPV triage 3y | 291 | 17.8215</td><td>3 yearly HPV with direct referral to colposcopy was most effective however at 2 times higher colposcopy rates (2’000 per 100’000 women)
3 yearly HPV with cytology triage was more effective than cytology with HPV triage with moderately increased colposcopy rates (830 /100’000 women)
Screening Strategy | Annual Cancer Incidence | QALY
HPV+cytology triage 3y | 163 | 17.8263
HPV only 3y | 145 | 17.8272</td><td>Cotesting was as effective as HPV with cytology triage</td></tr>
<tr><td colspan="3">The burden of screening was briefly discussed as number of expected colposcopies. QALYs had disutilities assigned to CIN and Cancer stages, but not to screening itself, being in triage or follow up.
The HPV only strategy had the highest colposcopy rates of 2000/100’000 women, while HPV with cytology triage or cotesting had 55-59% fewer colposcopy rates (830) compared to cytology based strategies with 160-700 colposcopies</td></tr>
<tr><td rowspan="2">Kulasingam et al. 2009 Canada [34]</td><td>The study did not have a comparator of cytology with HPV triage with 3-yearly frequency. The closest comparator to the Swiss strategy is 3-yearly Pap testing.

Strategy | Cancer cases | false positives
Pap test only 3y | 809 | 20’529</td><td>3 yearly and 5 yearly HPV testing with Pap triage starting at 25 years were more effective than 3 yearly cytology testing starting at 18 years

Strategy | Cancer cases | false positives
HPV + Pap triage 3y | 467 | 5’585
HPV + Pap triage 5y | 736 | 2’871</td><td>2 yearly cotesting was most effective (229 cancer cases, but with 82’340 false positive results)</td></tr>
<tr><td colspan="3">Concerning the burden of screening the number of false positive test results (Pap or HPV) was reported. HPV only (with direct referral to colposcopy) and 2 yearly cotesting of cytology and HPV (with direct referral to colposcopy if either test was positive) led to disproportionately high numbers of false positive tests</td></tr>
<tr><td rowspan="2">Bistoletti et al. 2008 Sweden

[75]</td><td>Three screening events at ages 32, 41 and 50 with cytology and HPV cotesting were more effective in terms of life years than 9 screenings with cytology (3-yearly from 32-50, then 5-yearly until age 60).
Adding HPV testing once at 32 years had no beneficial effect.

Life years
1. cytology | 29.67
2. added HPV testing once | 29.67
3. only 3x cotesting | 29.69</td><td>Not assessed</td><td>3 times cotesting dominated 9 times cytology based testing</td></tr>
<tr><td colspan="3">No data on the potential burden of screening (e.g. number of false positive results nor number of colposcopies were reported) nor were QALYs calculated. However it is likely that with only 3 screenings the burden of screening is lower or at least not higher than with 9 screenings</td></tr>
</table>

8 Results Research Question 1b "What is the best Age to start Screening with HPV tests in terms of clinical effectiveness and cost effectiveness?"

8.1 Summary Results Research Question 1b

In the combined follow up of four European RCTs, HPV based screening was found to have a strong protective effect in women between 30 and 34, however none in women younger than 30 years [39]. In younger women HPV based screening leads to more overdiagnosis than in older women [12, 47, 48]. Therefore most clinical systematic reviews and meta analyses recommend 30 years as the best starting age for HPV based testing. One systematic review considered 25 years based on the recent results of the ATHENA study [64].

Results on the optimal starting age from health economic studies are ambiguous. Most studies point at an optimal starting age of 25 or 30 years from a cost effectiveness standpoint and a balance of clinical benefit and burden of screening in terms of colposcopy rates.

8.2 Evidence on research question 1b from Clinical systematic reviews and meta analyses

Table 9 includes an excerpt of answers to research question 1b from clinical systematic reviews and meta analyses. The answers, the clinical background for this research question and available RCTs are summarized in the following paragraphs.

Screening young women with HPV testing has a different benefit-harm profile than that for older women. First, young women have a higher prevalence of regressive HPV infections, while in older women HPV infections are more often persistent and present therefore a higher risk for subsequent development of cervical cancer [90-92]. Second, for women of child bearing age any risk for complications during future pregnancies introduced by treatment of cervical lesions with conizations and LEEP must be minimized.

Therefore some RCTs were restricted to women older than 29 years (POBASCAM 29-60 years, Swedescreen 30-38 years), or they analyzed two age groups of younger and older women with partially different screening algorithms (e.g. in NTCC1 women younger than 35 years who tested positive for HPV but negative with cytology were invited for retesting after 12-18 months, while women of 35 years and older were sent immediately to colposcopy).

The phase 1 and 2 NTCC studies allowed comparison of HPV based versus cytology based screening algorithms between 2 age groups within one study. The authors of the study observed a high increase of cumulative detection of CIN2 and CIN3 in younger women and conclude that HPV testing in younger women leads to overdiagnosis and overtreatment [12]. Based on the data from NTCC the systematic reviews of Murphy [45] and Arbyn [44] state that HPV based testing in the age group between 25 and 34 will lead to higher detection of regressive CIN2.

The study of Ronco [39], which followed up all women participating in the RCTs NTCC, ARTISTIC, Swedescreen and POBASCAM, analyzed how many invasive cancer cases were detected per age group. They showed that the effect of reduced numbers of invasive cancer

was strong in women of 30-34 years at screen entry with 5/117'345 invasive cancer cases in the intervention group versus 15/102'598 in the control group. The protective effect of HPV based screening in these women was at least as high as in older women. Ronco et al. therefore conclude that screening with HPV testing should commence in women of 30 years. No protective effect was observed in women below 30 years at entry. In almost 90'000 women of this age group there were in total 5 cancer cases observed, of which 3 were in the intervention arm.

The systematic review of Rebolj [48] focused on the lower specificity of the HPV test compared to cytology and analyzed how many women will be diagnosed with a "false positive" screening result from their primary cervical screening test if this test is HPV versus cytology. A false positive screening result in this study is defined as the result of any primary screening test that leads to either retesting, triage testing of a secondary screening test or colposcopy and/ or biopsies, but is not associated with CIN3+. With the definition used in this study the frequency of false positive tests is increased with HPV testing at all ages, however the effect is more prominent in younger women than in women of 30 years and older (mostly based on the results of NTCC). The study comes to the conclusion that it is favorable to refrain from screening with HPV before the age of 30.

Pileggi [47] performed an analysis of the relative specificity and relative PPV of HPV based screening versus cytology based screening and found that over all age groups the relative specificity and PPV of HPV based screening was lower than with cytology based screening. For women of 30 years and older however, relative specificity and relative PPV were similar.

In contrast to the other systematic reviews, Huh considers starting HPV based screening at age 25 based on the results of the ATHENA cohort study that included women of 25 years and older [5, 64]. In ATHENA, approximately 30% of CIN3+ cases were found in women between 25 and 29 years of age. More than half of the women 25– 29 years of age with CIN3+ were found to have normal cytology. Starting HPV based screening with genotyping for HPV16/18 and reflex cytology for women with other hrHPV genotypes at 25 years of age, doubled the number of colposcopies but resulted in a 54% greater detection of CIN3+ when compared to the same strategy starting at 30 years of age [64].

Six further systematic reviews or meta analyses made a statement that HPV based testing should be restricted to women of 30 years and older based on existing current US screening guidelines and/ or the thought that in younger women HPV infections are more often transient than in older women [51, 52, 56, 67, 68].

This research question was not addressed by 4 systematic reviews or meta analyses [43, 46, 49, 65, 66].

8.3 Evidence on research question 1b from HTAs and Health Economic Studies

Table 10 in the Appendix includes an excerpt of answers to this research question from HTAs and health economic studies. The answers are summarized in the following paragraphs.

Only 6 health economic studies addressed the research question about the optimal age to start HPV based screening.

When a starting age of 30 or older was compared, there was a tendency to favor the younger age as a starting age. Goldhaber-Fiebert found that 30 years is more cost effective than 35 years [35] and Berkhof found that 31 years dominated 34 years [79]. In the study of Kitchener, 30 years dominated 35 years [2], while van Rosmalen found 32 years as the threshold for cost effectiveness [31].

When starting ages below 30 years were analyzed, 3 studies came to the conclusion that younger ages are not cost effective: de Kok found screening with HPV below 30 years was not cost effective [80], van Rosmalen found screening with HPV below 32 years was not cost effective [31] and Goldhaber-Fiebert found 30 years was more cost-effective than 25 years [35]. On the other hand Kitchener came to the conclusion that 25 years was more cost effective than 30 years, however with elevated colposcopy rates in younger women [2]. Kulasingam only compared 25 years and 18 years and favored 25 years as the starting age [34].

Two other studies had 25 years at the starting age and did not compare other options [29, 76].

9 Results: Research Question 1c, cost effectiveness of HPV based screening

For this research question 13 health economic publications had sufficient detail of result reporting, had a comparator of at least 3 yearly cytology testing and were therefore included into the quantitative analysis for research question 1c [2, 28-30, 32-37, 60, 75, 76].
One paper is an English publication of the central results from a German HTA. The 2 publications are henceforth referred to as 1 study [30, 60].

All studies included direct medical costs for the screening test, follow up diagnosis, treatment of precancerous lesions and cervical cancer. Some studies included additional costs such as cost for travel and time of women, costs for the organization of a screening program (invitations, registrations), or other costs as mentioned in the relevant chapters.

All detailed results on the cost and incremental cost effectiveness ratios of all studies and relevant strategies are shown in the Appendix in Table 10.
A condensed overview of the cost effectiveness of the most important strategies is shown at the end of this chapter in Table 6.

9.1 Summary of Health Economic Evidence Questions 1c

9.1.1 Synthesis cytology based testing

Cytology based testing was dominated by HPV based strategies in 9 out of 13 studies. In the remaining 4 studies cytology was less effective and cheaper.

Cytology based testing was dominated by HPV based strategies in 9 out of 13 studies. In the remaining 4 studies cytology was less effective and cheaper. In these cases HPV based strategies were either dominant or cost effective at higher ICERs.
Whether cytology based testing was dominated or on the cost effectiveness frontier depended in 1 study on the assumed sensitivity for cytology based testing and in another on the price of HPV testing: In the German study [60] 3 yearly cytology based testing was less effective but cheaper than HPV based testing (where sensitivity of cytology was taken from international studies), but dominated in a scenario with lower sensitivity values for cytology as observed in German studies. In Belgium [28] cytology based testing was dominated in the base case, and less effective but cheaper when higher HPV test prices were assumed (58 € instead of 35 €).

9.1.2 Synthesis HPV with cytology triage

HPV with cytology triage is the most researched and most often recommended cost effective strategy.

HPV with cytology triage was more clinically effective than cytology based testing if applied at the same frequency in 11 out of 11 studies. In 9 out of 9 studies it was also more effective or similarly effective if applied at lower frequencies than cytology based testing (e.g. 5 yearly instead of 3 yearly).
In 7 of the 11 studies HPV with cytology triage was not only more effective but also cheaper and thus dominated cytology based testing. In 4 studies HPV with cytology triage was more expensive with an ICER of 9’000 Euro/LYG (3-yearly [30, 60], Germany), 33’000 Australian

$/LYG (5 yearly [29], Australia), 12'300 Canadian $/QALY (3 yearly [33], Canada) and 51'000 US $/QALY (3 yearly [37], USA).

9.1.3 Synthesis HPV with partial genotyping for HPV 16 /18

HPV with partial genotyping for HPV 16/18 was clinically highly effective and always on the cost efficiency frontier. In 2 studies it was more effective and had higher ICERs than HPV with cytology triage, in 2 studies it dominated (directly or by extended dominance) HPV with cytology triage.

HPV with partial genotyping was analyzed in 4 studies. In this strategy women with an initial positive result for HPV 16 or 18 are directly transferred to colposcopy and women positive for other hrHPV types are referred to cytology triage.

In 2 studies HPV with genotyping was on the cost efficiency frontier with higher ICERs compared to HPV with cytology triage of 34'000$/QALY [36] (USA) and 100'000 Australian $/QALY [29] (Australia).
In 1 study HPV with genotyping dominated HPV with cytology triage at an ICER of 7'667 $/QALY [37] (USA, ICER compared to cytology with HPV triage).
In the UK study HPV with genotyping had an ICER of 15'000£/LYG or 30'000£/LYG depending on the frequency of follow up of HPV+/cyt- women [2] (UK, ICERs against the mixed strategy described below).

The UK study [2] in addition evaluated a mixed strategy. In this strategy primary screening was done 6 yearly using HPV testing with cytology triage. HPV positive/ cytology negative women were retested after 24 months or 12 months with HPV16/18 genotyping. Positive women were then directly transferred to colposcopy and women positive for other HPV types received cytology triage again. This strategy was also on the cost effectiveness frontier at an ICER of 10'000£/LYG (24m follow up) or 20'000£/LYG (12 months follow up).
In comparison to the strategies of HPV genotyping and the mixed strategy, HPV with cytology triage suffered extended dominance [2].

9.1.4 Synthesis Cotesting

Cotesting is clinically more effective than cytology based testing, however not cost effective when compared to other HPV based strategies.

Cotesting was assessed in 10 studies.
Cotesting dominated cytology based testing in 2 studies [75, 77], where no other HPV based strategy was analyzed. No ICERs could be derived from these two studies.
When cotesting was compared to other HPV based studies (8 studies), cotesting was dominated in 5 out of 8 studies. In the remaining 3 studies cotesting was on the cost effectiveness frontier with an ICER (against HPV with cytology of 17'204 US $/QALY [36], or at very high ICERs above an acceptable threshold of far beyond 100'000 $/QALY [35], [34].

9.1.5 Synthesis HPV with direct referral to colposcopy

HPV testing with direct referral to colposcopy is clinically effective, however strongly elevates colposcopy rates. Cost effectiveness results vary between studies.

This strategy was modelled in 3 studies and was dominated in 2 of the 3 studies by HPV with cytology triage [76] [34]. In the 3rd study HPV testing with direct referral to colposcopy was the most cost effective strategy at 11'400 Canadian $/LYG [33]. However it had double the colposcopy rates compared to the moderately more expensive study of HPV with cytology triage with an ICER of 12'300 Canadian $/QALY. (Both ICERs were calculated against cytology with HPV triage).

9.1.6 Differences between ICER values of seemingly similar strategies

While there is a consistent picture that HPV based screening will likely be cost effective, there are also considerable differences between the exact numbers for the ICERs found in the different studies for a seemingly similar strategy.

There was no correlation between ICERs and the cost of the HPV test or the relative cost between HPV or cytology test.

Different perspectives and costs taken into account may have an influence. In the Norwegian study in addition to direct medical costs, productivity costs of women during screening, diagnosis and follow up were included, which may have led to higher ICERs.

While it is obvious that the variation of the screening interval of the primary screening strategy has a big impact on clinical effects and costs, also variations in the follow up of HPV+/cyt- women had a strong effect. As an example in the UK study, variations in the follow up time after an initial HPV positive/ cytology negative result from 24 months to 12 months increased the ICER of the strategy by a factor of 2.

The use of QALYs instead of LYG potentially may better reflect benefits and burden of screening than LYG and lead to different costs. However the use of QALYs was applied very differently between studies. In some studies disutilities were only assigned to cancer stages [35, 76]. In this case QALYs are reduced only by mortality and incidence of cervical cancer. In others disutilities were also assigned to precancerous lesions. In this case a strategy that overdetects precancerous lesions will yield lower QALYs, thus also reflecting some burden of screening [33, 36, 37]. Some studies calculated QALYs with different sets of utility weights but due to the perceived unreliability of the results, relied on cost/LYG for their recommendations [2, 29]. Kulasingam also assigned disutilities in their sensitivity analysis to a false positive screening test result (but not to precancerous lesions). The rank order of strategies was not influenced in this case by using QALYs instead of LYG.

Within the same study QALYs must always be lower than LYG (otherwise the life years would not be quality adjusted). Thereby the use of QALYs will lead to lower clinical effectiveness numbers at the same cost and therefore have higher ICERs. Therefore it was analyzed whether studies that reported results only in cost/QALY versus cost/LYG had systematically higher ICER values. However between the different studies, there was no correlation between the ICER values and the use of QALYs or LYG.

The use of different discounting rates is known to influence the cost /LYG or /QALY [63] with higher discount rates leading to higher cost / LYG or /QALY.

There was no clear picture that studies with higher discounting rates had systematically higher ICERs than the other studies (Table 7). However there was one study [28] with a very low ICER of only 4'319 €/LYG for the strategy of 5 yearly HPV testing with cytology triage (in the scenario with a higher HPV test price of 58€). In this case discounting was higher for costs (3%) than for benefits (1.5%), which may have contributed to lower ICERs. The other studies had the same discount rate for costs and benefits.
However, the most likely explanation for the low ICER in this study is that the ICER was compared to 3 yearly cytology with HPV triage, which was a dominated strategy in most other studies. In those studies the HPV based strategies were compared to other HPV based strategies, which were slightly less effective than 3 yearly cytology based screening.

Table 6: Comparison of the cost effectiveness of the most important screening strategies

If not otherwise stated, ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study

Study, Country	Cytology based testing	HPV only or HPV with cytology triage	HPV testing with HPV16/18 genotyping	Cotesting
MSAC 2014 Australia [29]	Cytology only with 3 yearly testing from 25-49 years and 5-yearly from 50-64 was less effective and cheaper than HPV based testing. Other cytology based strategies were dominated	5 yearly HPV with cytology triage was more effective at an ICER of 33'000 Australian $/LYG	5 yearly HPV with HPV 16/18 genotyping was even more effective at an ICER of 100'000 Australian $/LYG	Dominated
Huh et al. 2015 USA [37]	Cytology with HPV triage was less effective than HPV based testing but cheaper	HPV with cytology triage was more effective than cytology based testing, but dominated by the genotyping strategy	3 yearly HPV with HPV 16/18 genotyping was the most clinically effective strategy at an ICER of 7'667 $/QALY (compared to cytology with HPV triage)	Dominated by HPV with cytology triage and by HPV with genotyping
Vijayaraghavan et al. 2010 USA [36]	Dominated	3 yearly HPV with cytology triage was more effective than 2-yearly cytology and cost effective at an ICER of 13'617 US $/QALY	HPV with 16/18 genotyping and cotesting with 16/18 genotyping was yet more effective at ICERs around 34'000$/QALY	3 yearly cotesting was less effective than genotyping, but cost effective at an ICER of 17'204 US $/ QALY
Kitchener et al. 2014 UK [2]	Dominated	6 yearly HPV with LBC triage dominated cytology based testing, but suffered extended dominance from HPV testing with HPV 16/18 genotyping and the mixed strategy described below	6-yearly HPV based testing with HPV 16/18 genotyping was most cost effective at 15'000 £/LYG (24 months follow up) or 30'000£/LYG (12m follow up)	dominated
		In a mixed strategy HPV with cytology triage was followed up with HPV16/18 genotyping for women persistently HPV+/cyt- after 12m. This strategy was cost effective at 20'000£/LYG (against immediate HPV 16/18 genotyping with 24m follow up)		

Study, Country	Cytology based testing	HPV only or HPV with cytology triage (no genotyping strategy was included)	Cotesting
Sroczynski et al., 2010, 2011, Germany [30, 60]	In the base case 3 yearly Pap testing was cost effective at 7'100 Euro / LYG against 5 yearly Pap testing. In the scenario with lower sensitivity values for cytology based testing (from German studies sensitivities it was dominated	In the base case with higher sensitivity of cytology based testing, 3 yearly HPV based testing had higher effectiveness than 3 yearly cytology based testing at an ICER of 9'000 Euro /LYG. 5-yearly testing with HPV based strategies were slightly more effective than 3 yearly Pap testing, however suffered extended dominance from a combination of 3 yearly Pap testing and 3 yearly HPV base testing. It is important to note that in the HPV based strategies, women below 30 years received 2 yearly Pap testing, which makes interpretation of the comparison to 3 yearly Pap testing more difficult. In the scenario with lower sensitivity values for cytology based testing (from German studies) 5 yearly HPV based testing was cost effective at 3'700 €/LYG (versus no screening) and 3 yearly HPV based testing was cost effective at 6'100 €/LYG (versus 5 yearly HPV)	Dominated
Arbyn et al. 2015, Belgium [28]	Dominated in the base case	In the base case 5-yearly HPV testing with cytology triage dominated 3 yearly cytology. If higher HPV prices (58 €) are assumed, cost effective at an ICER of 4319 €/LYG vs cytology	Not assessed
Accetta et al. 2010, Italy, [76]	Dominated	5 yearly HPV with Pap triage is more effective than 3 yearly Pap test at an ICER of 4'444 Euro/QALY, 3 yearly HPV with Pap triage is yet more effective at 68'421 Euro/ QALY HPV with direct colposcopy referral was dominated	Not assessed
Burger et al. 2012 Norway [32]	Dominated	6-yearly HPV with cotesting triage was less effective than 3 yearly cytology but cheaper ICER compared to no screening 29'000 Euro/LYG 5 yearly HPV with cotesting triage was more effective than 3 yearly cytology and cheaper at 57'000 Euro/LYG	Not assessed
Goldhaber-Fiebert et al. 2008, USA [35]	3 yearly cytology based testing was dominated	5 yearly HPV with cytology triage is more effective than 3 yearly cytology with HPV triage at 12'000 (start at 25y, switch to HPV testing at 35 years) or 29'000 $/QALY (switch at 30 years) 3 yearly HPV with cytology triage is yet more effective at ICER of 37'000 (25y,35y) or 53'000 (25y,30y) or 78'000 $/QALY (21y,30y)	Dominated or too costly (ICER > 3Mio $/QALY)
Vijayaraghavan et al., 2010 Canada [33]	3 yearly cytology with HPV triage was cost effective at 9'600 Canadian $/LYG (against no screening)	3 yearly HPV with direct referral to colposcopy was most effective and dominated all other strategies however at 2 times higher colposcopy rates (ICER 11'400 Canadian $/LYG) 3 yearly HPV with cytology triage was more effective than cytology with HPV triage with moderately increased colposcopy rates at 12'300 Canadian $/QALY (vs cytology with HPV triage)	Dominated
Kulasingam et al. 2009 Canada [34]	Dominated	3 yearly and 5 yearly HPV testing with Pap triage were more effective than 3 yearly cytology testing at ICERs of 6720 (against no screening) and 24257 Canadian $/LYG (against 5 yearly HPV with Pap triage) HPV with direct referral to colposcopy led to disproportionately high numbers of false positive tests and was not on the cost effectiveness frontier	2 yearly cotesting was on the cost effectiveness frontier with an ICER of 432'751 Canadian $
Bistoletti et al. 2008, Sweden [75]	Dominated	Not assessed	3 times cotesting dominated 9 times cytology based testing

9.2 Correlation of Results with Study Quality

No correlation of results with study quality was identified.

Study quality was assessed by application of the EURONHEED checklist. The results of all entries of the checklist and the overall quality data score and transferability data score are shown in the Appendix in Table 13.
Two publications were excluded from quantitative analysis based on insufficient detail of effectiveness results reporting (question E5). Quality data scores of the remaining publications ranged from 0.93 to 0.65.

When a comparison was done, whether certain screening strategies were only analyzed by studies with low or high quality data scores, no association was found. E.g. HPV with cytology triage was analyzed by almost all studies across all quality data scores. The second most important strategy with HPV 16/18 genotyping was analyzed by 4 studies ranging from the highest quality data score of 093, [37], over 0.89 [29] and 0.86 [2] to a comparatively low data score of 0.73 [33].

When ICERs of 5 yearly HPV screening with cytology triage were compared with the quality data score of the studies, there was a tendency to higher ICERs in studies with a lower quality data score. While this result should not be over interpreted, it is at least a hint that poorer study quality did not bias cost effectiveness results in favor of HPV based strategies.

As only 2 studies with HPV 16/18 genotyping were found potentially transferable to the Swiss Health system and only for these the ICERs were adapted to CHF no correlation between the quality data score and the ICERs were calculated.

9.3 Summary of the Transferability Analysis

Three studies have similar parameters to Swiss screening with results that may be transferable to the Swiss health system. Recommended strategies were 3 – 5 yearly HPV with cytology triage.
Two studies had lower screening frequencies for cytology based screening in women over 49 years. Costs for organized screening were added into the model. The results may become transferable if Switzerland decides to install organized screening in the future. The studies recommend HPV with HPV16/18 genotyping or HPV with cytology triage with 5 or 6 yearly frequencies starting at 25 or 30 years.
Two studies started modelling only at the age of 30. If additional costs for screening are added for younger women, one of these studies may be transferable to the Swiss health system. The study recommended 5 yearly HPV with cytology triage.
The results of 4 studies seem not to be transferable due to different treatment options or relevant differences in the primary screening strategy compared to the Swiss recommendations.
In 2 studies data were insufficient to conclude transferability

In order to assess how the cost effectiveness results might translate into the Swiss situation a transferability analysis was done.

For this research question the same 13 health economic publications were considered as for research question 1c [2, 28-30, 32-37, 60, 75, 76]. As described above 1 paper is an English

publication of the central results from another (a German HTA). The 2 publications are therefore referred to as 1 study [30, 60].

As described in the methods chapter 5.4, model parameters of each study were compared to the reference values for the Swiss health system. If differences were found for any of the relevant transferability parameters an estimation was done, of how this might influence the result of the model if the Swiss parameters had been used. The detailed results of all questions for the transferability analysis are described in Appendix 7: “Transferability Analysis for the health economic studies” in Table 14.

The transferability analysis showed that the studies with the most similar comparator to Swiss screening are those by Goldhaber-Fiebert (USA, [35]), Burger (Norway, [32]) and Sroczynski (Germany, [30, 60]). The results of these studies may be transferable to the Swiss setting.

Goldhaber-Fiebert (USA) [35] showed results for 3 yearly cytology with HPV triage with starting ages of 21 or 25 years and modelled a switch to HPV based testing at ages of 30 or 35 years. Treatment strategies seem to be close and HPV prevalence data slightly lower than in Switzerland [62]. It was found that the order of strategies in terms of clinical and cost effectiveness were independent of attendance rates. 3 yearly and 5 yearly HPV with cytology triage were recommended cost effective strategies.

Burger (Norway) [32] showed results for 3 yearly cytology with cotesting triage starting at 25 years and switching to HPV based strategies at 31 years. Treatment strategies seem sufficiently close to Swiss recommendations. No HPV prevalence data were available. 4 or 5 yearly HPV based testing with cotesting triage were the recommended strategies in this model.

Sroczynsky (Germany) [30, 60] showed results for 3 yearly cytology with HPV triage and modelled strategies switching to HPV based strategies at 30 years. Screening, follow up and attendance rates seem sufficiently close to the Swiss situation. No HPV prevalence data were available. 3 yearly HPV based screening was a cost effective recommended strategy.

The following studies had slightly different frequencies for screening than in Switzerland.

The studies of Kitchener (UK) [2] and MSCA (Australia) [29] modelled cytology with HPV triage screening starting at 25 years with 3 yearly screening until 49 years followed by 5 yearly screening for older women. Treatment options seem to be similar. The background HPV prevalence in Australia seemed to be lower than in Switzerland. In the UK HPV prevalence was higher than in Switzerland until the age of 40. Big differences in HPV prevalence were found in the UK between different cities. In the UK cancer incidence rates of women between 25 and 35 years of age are much higher than in Switzerland. Both countries have organized screening programs. Different attendance rates were modelled both for primary screening as well as for triage tests and colposcopies. It was found that ensuring compliance with follow up colposcopies is important to ensure effectiveness of HPV based strategies. All strategies including those that were HPV based started at 25 years.

Even though in one study prevalence is higher and in the other lower than in Switzerland, the studies come to the same conclusions regarding recommended strategies. Therefore prevalence may not negatively affect the transferability of these studies.
Both models come to the same conclusion that HPV with HPV16/18 genotyping is the most clinically and cost effective strategy followed by HPV with cytology triage (either 5 or 6 yearly).

The following studies only modelled screening starting ages of 30 years. These strategies may therefore start with a higher background risk than in Switzerland and they may be cheaper and less effective than current Swiss screening. The results are however still interesting for a comparison of cytology based and HPV based strategies after the age of 30 years. If in Switzerland cytology based screening for younger women is maintained and a switch to HPV based strategies considered at the age of 30 years, the cost for screening in younger women would have to be added to both intervention and comparator strategies in the models.

Among these studies the Belgian study is probably closest to the Swiss situation. Arbyn (Belgium) [28] modelled cytology with HPV triage with 3 yearly frequencies. All CIN stages seem eligible for treatment. HPV prevalence is higher in Belgium than in Switzerland (which would rather favor cytology based screening [80]). Attendance rates were modelled between 40 and 80% which likely includes Swiss attendance rates. 5 yearly HPV with cytology triage was more clinically and cost effective than cytology based screening.

Due to different treatment options for CIN2 and the assumption of 100% compliance the results of the study of Huh [37] may not be transferable to the Swiss context

Huh (USA) modelled 3 yearly cytology based screening with HPV triage and compared it to various HPV based strategies. Treatment options seemed not to include CIN2 treatment which is different from Swiss recommendations. HPV prevalence was assumed slightly lower than in Switzerland. 100% compliance with primary screening and follow up was modelled, thus showing the maximum possible cost and benefit of strategies. However, real life effectiveness and cost will be lower. HPV with HPV 16/18 genotyping dominated all other strategies in this study.

For the following publications data are insufficient to conclude transferability.
Vijayaraghavan (Canada) [33] modelled 3 yearly cytology testing with HPV triage for younger women and switching to HPV based strategies starting at 30 years. Treatment options were only available in referenced supplementary materials that were impossible to retrieve from the author despite several attempts. HPV prevalence was similar in women of 30-39 years, and lower for older women in Canada than in Switzerland [62]. Attendance rates were varied. This did not change the relative cost effectiveness of the screening strategies. With similar treatment patterns the study results would be transferable. 3 yearly HPV only and HPV with cytology triage were clinically more effective at slightly higher ICERs than 3 yearly cytology with HPV triage.

Accetta (Italy) [76] modelled 3 yearly cytology testing with HPV triage from 25-65 years however follow up after primary screening tests was not described. Treatment options seem not to include CIN1 treatment. HPV prevalence is comparable to Switzerland. Average

compliance rates of 70% were assumed. Sensitivities of cytology and HPV tests seem to be rather favorable for cytology based screening. Under the assumption that the follow up after cytology testing with HPV triage is similar as in Switzerland the results of the study may be transferable. 5 yearly HPV with cytology triage was found clinically and cost effective.

The following studies were excluded from further transferability analysis due to comparator strategies that were considered not close enough to the current Swiss strategy.

In the Swedish study of Bistoletti [75] the follow up after a primary screening test results (cytology) was not described. Therefore it is not clear whether the strategy is close enough to Swiss recommendations. In addition the study mentioned that Swedish cytology screening may be less sensitive than in other countries. This would favor HPV based testing. In this study 3 times cotesting in a woman's life was more clinically and cost effective than 3 yearly cytology between 32 and 50 years followed by 5 yearly cytology. It is unclear whether these strategies would compare equally in the Swiss situation.

The study of Vijayaraghavan (USA) [36] had shorter screening frequencies (2 yearly) in their cytology based screening strategy than the recommended Swiss 3 yearly intervals. It is assumed that this strategy is more costly than the current Swiss strategy and economic results will not be transferable. Cytology based strategies were dominated by HPV based strategies.

The study of Kulasingam [34] had a 3 yearly Pap testing strategy, but without HPV triage. Annual Pap testing with HPV triage was also modelled. This strategy is most probably much more expensive than current Swiss screening and results will not be transferable.

9.4 Deduction of costs and cost effectiveness values in CHF by adaptation using purchasing power parities

Five yearly HPV with cytology triage dominated cytology based screening in 4 out of 5 studies. It resulted in ICERs between 6'862 CHF/LYG (against 3 yearly cytology based screening) and 56'723 CHF/QALY (against 6 yearly HPV with cytology triage). In all studies this strategy was more effective than 3 yearly cytology based screening.

Three yearly HPV with cytology triage was on the cost effectiveness frontier in 3 potentially transferable studies with ICERs between 17'450 CHF/LYG (against cytology based screening), 96'192 CHF/QALY (against 5 yearly HPV with cytology triage) and more than 100'000 CHF/LYG (against 4 yearly HPV with cytology triage).

HPV testing with genotyping for HPV 16/18 was cost effective in 2 potentially transferable studies at ICERs (against HPV with cytology triage of the same frequency) between 32'171 CHF/QALY and 89'961 CHF/LYG.

None of the studies provided results in a way that allowed direct adaptation of the results into Swiss values (e.g. by providing cost and units for all aspects). Therefore it was only possible to translate values for cost and cost effectiveness ratios into CHF/LYG or /QALY by adaptation to purchasing power parities. While this rather simple transformation cannot reflect the true costs in Switzerland, the values in CHF show better where the potential costs in Switzerland might be than the values in the currency of another country. They also make values of different studies more comparable by using the same currency and cost year. An overview of all deducted values is shown in Table 15.
In this chapter only the results for strategies with potential transferability are shown (Table 7). In summary, the following results were achieved:

5 yearly HPV with cytology triage dominated cytology based screening in 4 out of 5 studies. It yielded ICERs between 6'862 CHF/LYG (against 3 yearly cytology with HPV triage) and 56'723 CHF/QALY (against 6 yearly HPV with cytology triage) in the studies from Belgium [28], Australia [29], UK [2], the US [35], and Norway [32]. In all these studies 5 yearly HPV with cytology triage was more effective than 3 yearly cytology.
In the base case of the German study [30, 60] with high sensitivity of the Pap test, 5 yearly HPV with cytology triage suffered extended dominance from the combination of 3 yearly Pap testing and 3 yearly HPV based testing. In the scenario with German (lower) sensitivity values of the Pap test, 5 yearly HPV with cytology triage dominated cytology based testing and had an ICER of 6'786 CHF/LYG against no screening. It is important to note that in this study HPV based screening strategies involved 2 yearly Pap based screening for women below 30 years, which increased the cost of HPV based screening strategies compared to 3 yearly cytology.

3 yearly HPV with cytology triage had an ICER of 17'450 CHF/LYG (against 3 yearly Pap testing) in the German study [30, 60] and in a US study of 96'192 CHF/QALY (against 5 yearly HPV with cytology triage) [35].
A threshold of 100'000 CHF/LYG was exceeded by 3 yearly HPV with cytology triage in the study from Norway [32], where this strategy was compared to 4 yearly HPV with cytology triage. The Norwegian study included more costs into the model than others by adding the cost for women's time for screening, diagnosis and follow up into the calculation. In addition

the follow up time of HPV positive/ cytology negative findings was short with only 6 months compared to 12 months or more in other models. (For comparison with the German study: had the ICER been calculated against 3 yearly cytology based screening it would have been below 40’000 CHF/LYG.)

HPV testing with genotyping for HPV16/18 yielded ICERs (against HPV with cytology triage of the same frequency) of 21’447 CHF/LYG in the UK with 6 yearly screening and 24 months follow up time or 64’342 with 12 months follow up time [2], and with a 5 yearly screening frequency in the Australian study of 89’961 CHF/LYG [29].

Costs of cytology and HPV tests from the studies were also translated into CHF by adaptation to purchasing power parities and are shown in Table 7. The numbers can give an impression how close the test cost assumptions in the models are to Swiss costs. Cytology costs varied from 11 CHF to 71 CHF. HPV tests were varied between 20 and 92 CHF. The cost of cytology testing in Switzerland is within that range. For HPV testing no price for primary screening is fixed yet for Switzerland. Also after conversion of local currency costs into CHF by adaptation to purchasing power no correlation was found between ICERs and HPV test costs (the correlation factor of the HPV test cost to the ICERs was -0.11).

Table 7: Test Costs and ICERs translated into 2015 CHF by adaptation using purchasing power parities

A footnote was added that explains which strategy the ICERs was calculated against. If no footnote is added, the ICER was calculated against the next more cost effective strategy shown for the study in this table. An overview of all relevant strategies and their relative effectiveness and ICERs in original currency can be found in Table 10.

Study	Cytology test	HPV test	Discount rates (%) Cost/ benefits	ICERs 3-yearly HPV testing	ICERs 5 yearly HPV testing (Kitchener 6 yearly)
Arbyn, [28], Belgium	35 CHF (52 if 2nd reading necessary)	56 CHF up to 92 CHF	3 1.5		Cytology was dominated in the base case With an HPV test price of 92 CHF the ICER of HPV with cytology triage = 6'862[2] CHF /LYG
Goldhaber-Fiebert, [35],USA	55 CHF	100 CHF	3 3	Cytology based testing was dominated. HPV testing with cytology triage = 96'192[3] CHF/QALY	Cytology based testing was dominated. HPV with cytology triage = 52'634[4] CHF/QALY
Sroczynski, [30] Germany	71 CHF	101 CHF (thereof 42 for the test)	3 3	3-yearly HPV based screening (where most of the HPV positive samples were followed up with cytology triage) = 17'450[5] CHF/LYG (base case) and 11'827 CHF/LYG (scenario with lower sensitivity of Pap test)	Dominating cytology in the scenario with lower sensitivity of the Pap test at 6'786 CHF/LYG versus no screening
Burger, [32], Norway	50 CHF	62 CHF	4 4	Cytology based testing was dominated. HPV testing (6 month follow up time of HPV+/cyt- women) > 100'000[6] CHF/LYG.	Cytology based testing was dominated. HPV with cytology triage(12 months follow up) = 56'723[7] CHF/LYG
MSAC, [29], Australia	54 CHF	64 CHF	5 5		HPV with cytology triage = 29'687[8] CHF/LYG. HPV with16/18 genotyping = 89'961 CHF/LYG.
Kitchener, [2], UK	11 CHF if negative 32 CHF if positive	20 CHF	3.5 3.5		Cytology based testing was dominated HPV with LBC triage (after 24m HPV 16/18 for women persistently HPV+/cyt-) = 21'447[9] CHF/LYG HPV16/18 (24m follow up) 32'171 CHF/LYG HPV with LBC triage (after 12m HPV 16/18 for women persistently HPV+/cyt-) = 42'895 CHF/LYG HPV16/18 (12m follow up) = 64'342 CHF/LYG

[2] Against 3 yearly cytology with HPV triage

[3] Against 5 yearly HPV with cytology triage

[4] This strategy dominated 3 yearly cytology. The ICER was calculated against the next less effective strategy on the cost effectiveness frontier (5 yearly HPV with cytology triage, with a switch from cytology to HPV based testing at 35 years instead of 30 years, which was less effective than cytology based testing)

5 Against 3 yearly Pap testing

[6] Against 4 yearly HPV with cytology triage (6 months follow up time)

[7] This strategy dominated 3 yearly cytology. The ICER was calculated against the next less effective strategy on the cost effectiveness frontier (6 yearly HPV with cytology triage, 12 months follow up time, which was less effective than cytology based testing)

[8] Against 3 yearly cytology at ages 25-49 and 5 yearly cytology at ages 50-64

[9] This strategy dominated cytology based CP. The ICER was calculated against the next less effective strategy on the cost effectiveness frontier: HPV with LBC triage (after 24m HPV 16/18 for women persistently HPV+/cyt- with 10 yearly frequencies for women >50 years, which was less effective than CP)

10 Results Research Question 2: Feasibility of HPV based primary cervical cancer screening

No hard barriers were identified for the implementation of HPV based cervical cancer screening. The most important concern raised was that adherence to screening algorithms and quality control should be ensured by appropriate measures, e.g. by implementation of an organized screening setup. Active stakeholder management of GPs/ gynecologists should be considered and communication tools provided to ensure that women receive the necessary information on cervical cancer screening with HPV and to minimize psychosocial distress.

10.1 Extraction of answers from publications

Answers to research question 2 were extracted from 36 publications (clinical systematic reviews and meta analyses as well as HTAs and health economic studies), according to the algorithm described in the methods chapter 5.5. Answers were then classified into "concern categories" and focus areas identified based on the frequency that the different concerns were mentioned. All detailed information retrieved and the associated concern categories are displayed in Table 11 and Table 12. The results are summarized in the following paragraphs ordered by the frequency a concern was raised across publications:

10.1.1 Adherence to Policy

Ensuring adherence to policy is the predominant concern of 16 publications [2, 28, 30, 35, 37, 44, 46, 51, 52, 60, 65, 67, 68, 78, 80, 81]. It is clear that the projections of models will only translate into the same level of clinical and cost effectiveness, if the strategies are indeed implemented as modelled. If age restrictions for HPV testing, screening frequencies and follow up recommendations are ignored, a less specific primary screening test may lead to more overdiagnosis and overtreatment.

Special attention should be put on the adherence to follow up schedules for HPV positive/ cytology negative women as cited by 5 publications. If these women are lost to follow up, the benefit of the superior sensitivity of the HPV test could be eroded [2, 28, 31, 32, 45].
One detail in HPV testing with cytology triage is the question how to sample for the triage test. van Rosmalen et al. [31] compared sequential sampling, where women with a positive HPV test are invited for a second visit to take the triage test sample, to concurrent sampling, where the triage test sample is always taken together with the sample for the HPV screening test but only analyzed if the HPV test is positive. Concurrent sampling has been found more cost effective. The additional cost of collecting the cytology sample was outweighed by the combined benefits of not losing HPV positive women at this stage of the screening algorithm and avoiding the cost for a second visit.

Both health care professionals as well as women themselves influence adherence. Whitlock questioned whether policy will be accepted by (US) physicians [68] and Schiffman pointed to evidence that in the US current evidence-based guidelines for cervical cancer screening and management are being widely ignored [52] [93].
Women's preferences are important as some women may feel insecure about longer screening intervals as mentioned by 2 publications [30, 37]. Prolongation of screening intervals may be perceived by women as a money saving activity of policy makers [30]. Therefore, when policy is changed to longer screening intervals, this needs to be accompanied by proper information about the benefits of longer screening intervals.

10.1.2 Organized Screening Setup

The concerns addressed in the previous chapter led to the recommendation to implement HPV based screening in an organized screening program (10 publications [29, 30, 44-46, 49, 60, 65, 81]), where adherence to recommended practice and many of other concerns listed here can be better controlled.

10.1.3 Piloting, Monitoring and Evaluation

Ongoing monitoring and evaluation whether the expected outcome is achieved is recommended in 9 publications [30, 32, 46, 49, 56, 60, 65, 74, 81] (thereof 5 publications are from Germany). This measure allows the timely identification of issues in the implementation of a screening program and targeted actions to address these.
In order to verify that all practical implementation aspects have been fully and effectively addressed, a pilot project should be done before roll out of HPV based screening as recommended by 7 publications [2, 30, 46, 60, 65, 79, 81] in line with European Guidelines for Quality Assurance in Cervical Cancer Screening [94].

10.1.4 Quality Control, validated HPV tests

Quality control of all aspects of cervical cancer screening is recommended by 7 publications [28-30, 46, 60, 65, 81].
The most critical quality control step is that only clinically validated HPV tests must be used, which have proven sensitivity and specificity as seen in RCTs and assumed in models. This recommendation was emphasized in 6 publications [28-30, 54, 60, 64, 81].

As an advantage of HPV based screening it was stated that quality control of HPV tests may be easier than that for cytological testing due to the higher degree of automation and standardization of HPV tests [28].
To further strengthen quality control the implementation of a central reference laboratory for HPV testing was recommended by 1 publication [28]. [10]

10.1.5 Call/ Recall Systems

To improve adherence of women to screening and follow up schedules, 4 publications recommended implementation of a call/ recall system that consists of invitations and reminders if invitations are missed [29, 30, 45, 60].

10.1.6 Communication

Appropriate communication about HPV based screening and the significance of a positive test result, especially in conjunction with a negative cytology result, was mentioned by 2 publications [28, 45]. One of these recommend the development of a standardized patient leaflet to ensure that all women receive the same scientifically based information [28].

10.1.7 Psychosocial aspects

As HPV infections occur through sexual interactions, a positive HPV test result has the connotation of a sexually transmitted disease. This may involve stigma and lead to insecurity in sexual behaviors and questions about relationships [49, 56]. The presence and amount of stigma related to a sexually transmitted infection differs between cultural backgrounds and requires special consideration to ensure that all women in a society can participate in and benefit from the screening program to the same extent [49].

[10] A reference laboratory already exists in Switzerland

More research into how a positive HPV test results affects quality of life was recommended by 2 publications [2, 30].

10.1.8 Effects on health care professionals

HPV based testing algorithms were found more complex than cytology based algorithms by 2 publications [32, 52] and as such require special education of health care professionals [49, 52]
Two publications mentioned that longer screening intervals may be perceived as an economic threat to GPs or gynecologists [30, 52]. Fewer visits to the doctor was seen as positive in the Australian publication [29] as it freed resources for other activities.
Also if screening activities should be centralized (either sampling, testing or communication) the role of GP/ gynecologist as a central point of contact and information for women's health would change [28].

10.1.9 Side effects on other aspects of women's health

In the German publications there was a concern about the potential side effects of longer screening intervals on regular attendance at gynecological checkups [30, 46, 65].

10.1.10 Practical implementation aspects

Several practical implementation aspects were noted:

A central database containing the screening data of all eligible women and enabling both call/ recall systems as well as monitoring and evaluation of the screening program was an important aspect mentioned by 2 publications [29, 30].
Reimbursement policies need to be adapted [67] so that all women have access to the new technology regardless of socioeconomic background. It is also recommended that reimbursement policies be defined in a way that enforces adherence to screening algorithms [28].
Resource availability needs to be ensured according to the needs of the new technology [33].
Two publications recommended centralization of laboratory services to achieve economy of scale and better prices for the HPV testing [80, 81].

10.1.11 Address the underscreened, self-sampling as opportunity

Finally 4 publications noted that the introduction of a new technology will not solve the problem that a high amount of cervical cancers occur in women who never attend screening or attended less often than recommended [35, 51, 64, 67]. E.g. in the US half of the women with cervical cancer have never participated in cervical cancer screening and another 10% had their last cytological screening test more than 3 years ago [67]. 1 additional publication recommended to use the money saved by implementing HPV based screening to target women who previously did not attend [76].
One publication saw a benefit of HPV based screening for women attending infrequently as they will have longer protection against cervical cancer with a negative HPV result than with a negative cytology result.
Self-sampling of cervical smears for HPV analysis was suggested in 4 publications [28, 29, 49, 67] as a method to reach women who do not see a gynecologist for reasons of shame, stigma, no time for a visit or other social reasons. Indeed, self-sampling is implemented in the new HPV based Dutch cervical screening program for women who otherwise would not

attend screening [28]. It is also recommended for implementation for underscreened women in Belgium [28] and in Australia [29].

10.1.12 No concerns

Eight publications expressed no implementation concerns [34, 36, 43, 47, 48, 66, 75, 77] (partly due to their focus on specific research questions that did not contain implementation aspects).

10.2 Relevance for the Swiss Health Care setting

The identified concerns for implementation are relevant for the Swiss context, as screening in Switzerland is opportunistic and implementation of clinical guidelines in ambulatory care is currently not systematically enforced nor is adherence to policy systematically monitored.
In Switzerland health care professionals are the most important source of information on cervical cancer screening for the eligible women and have a big impact on the trust of women in the screening program and their adherence. Therefore it will be important to obtain the support of the affected health care professionals for a potential policy change.

In case of a switch to HPV based screening in Switzerland, measures should be implemented to address the concerns as described in chapters 11.2 and 11.4.

11 Discussion

The discussion chapters 11.1 and 11.2 evaluate the evidence for the hypotheses of this master thesis. The answers to each research question are briefly summarized and any inconsistencies are discussed and evaluated. Chapter 11.3 addresses the limitations of this thesis and in chapter 11.4 conclusions are drawn for potential policy changes for the Swiss health system.

11.1 Hypothesis 1

The evidence found in this thesis confirms hypothesis 1: The use of HPV as the first line screening test improves clinical effectiveness of cervical cancer screening at lower screening frequencies and is cost effective.
A 5 yearly strategy of HPV based screening with cytology triage seems ideal for women of 30 years or older. In younger women cytology based testing should be maintained. Women with HPV positive/cytology negative results should be retested after 12 months. This strategy is likely to reduce the incidence of cervical cancer without increasing the burden of screening – or even reducing the burden of screening by having longer screening intervals.
Alternatively a strategy with 5 yearly HPV 16/18 genotyping can be recommended with direct referral to colposcopy for HPV16/18 positive women and cytology triage for other hrHPV types.
From a health economic perspective the above mentioned HPV based cervical cancer screening strategies may be either cheaper than cytology based testing or cost effective at ICERs below acceptable threshold.
Cotesting is not a recommended strategy from a health economic perspective.

11.1.1 Research Question 1a: What is the best test or combination of tests which results in the highest clinical effectiveness to prevent cervical cancer at the lowest burden of follow up?

Agreement is strong across systematic reviews and meta analyses, that HPV based screening is more sensitive than cytology and thus more effective to identify women with precancerous lesions. These women can then be properly surveilled and treated before cervical cancer develops. The combined follow up of the 4 European RCTs was powered enough to show a significant decrease of cervical cancer incidence by HPV based testing. The effect was strongest in the NTCC trial with direct referral of hrHPV positive women to colposcopy, followed by Swedescreen and POBASCAM and weakest in ARTISTIC. In the latter study it was discussed that as a comparator LBC was used with an unusually low positive threshold which resulted in unusually high sensitivity and lower specificity in the cytology arm of the study. This explanation seems plausible.

The downside of the HPV assay is its lower specificity compared to cytology. As only persistent HPV infections may lead to cancer, and many infections are cleared by the immune system within one or two years, many positive HPV results will not be associated with advanced precancerous lesions or cancer (CIN3+). Therefore several studies analyzed whether HPV testing will lead to more false positive results and overdetection of early precancerous lesions.

This aspect has been addressed by meta analyses that measured relative detection rates of CIN2+ and CIN3+ over 2 screening rounds. Based on the fact that cumulative detection

rates of CIN2+ and CIN3+ were the same with HPV with cytology triage but higher with direct referral to colposcopy, all but one study came to the conclusion that direct referral to colposcopy after every HPV positive result led to overdetection of precancerous lesions, while HPV with cytology triage did not. One study concluded that only with direct referral to colposcopy did HPV based screening have increased sensitivity compared to cytology based screening [66].
This thesis cannot follow this conclusion, as also in the RCTs POBASCAM and Swedescreen, which did not refer HPV positive women directly to colposcopy but used an HPV with cytology triage approach, cervical cancer incidence rates were reduced [39]. Therefore overdetection of precancerous lesions by direct referral to colposcopy is considered the more likely explanation of the results.

The study of Rebolj found that the rate of “false positive” results is elevated with HPV based testing compared to cytology based testing. In this case a positive result was any result leading to triage, retesting after shorter frequencies or colposcopies and not associated with a CIN3+ finding. The author assumed that the rate of false positive results over the life time of a woman may be more similar, if longer screening intervals are adopted with HPV based testing.
This thesis comes to the conclusion that the definition of a false positive result in this study is very narrow. It will be important to effectively communicate the significance of a positive HPV result to the affected women, so they understand that an HPV infection is a risk factor that indicates closer surveillance rather than “having cancer” or a precancerous lesion.

At the same time the risk of overdetection of precancerous lesions is real if women are screened for HPV at too young an age, as in this cohort HPV infections are more often transient than persistent (see also research question 1b). Also in older women too short screening intervals bear the risk of identifying more transient HPV infections. Therefore with HPV based screening it is important to adhere to recommended screening intervals to balance benefits and harms.

Systematic reviews criticized all RCTs for incomplete reporting on colposcopy rates. Therefore data on colposcopy rates are mostly based on modelling.
Modelling data show that colposcopy rates of HPV with cytology triage are either lower or moderately higher than with cytology based screening. Based on the data this thesis comes to the conclusion that colposcopy rates are likely to be in a comparable range to current policy.
Colposcopy rates were higher with the HPV16/18 genotyping strategy along with higher clinical effectiveness. Studies came to different conclusions about how much colposcopy rates will be elevated. To date this strategy has been less frequently researched. The evidence on partial genotyping can therefore be considered emerging. However when analyzed it was always found more effective than cytology triage. Most convincingly, cohort studies show that the CIR to develop CIN3+ over 3 years is higher for HPV16/18 but cytology negative women than for women positive for other hrHPV types and positive for cytology [71]. This shows that HPV16/18 genotyping increases the specificity of the screening algorithm more than cytology triage.

In meta analyses cotesting did not have a relevant benefit over HPV with cytology triage [28]. One systematic review raised the concern that issues with HPV sampling might lead to

false negative results not being identified in test internal controls, which could be detected by cotesting with a cytology sample. No concerns about false negative results with HPV testing due to sampling issues have been reported in any other systematic review. It is therefore concluded that this is not a widespread concern. Nevertheless this is a topic that must be addressed during the clinical evaluation of HPV assays that are approved for use in primary screening.

11.1.2 Research Question 1b: What is the best age to start using HPV as primary screening test in terms of clinical effectiveness and cost effectiveness?

Thirty years seems to be a reasonable choice for the age to start HPV based screening.

As only persistent HPV infections lead to cancer and most HPV infections in young women are cleared quickly by the immune system [95], it is important to find a balance between identification of women at risk to develop cancer and avoidance of unnecessary anxiety, follow up tests or treatment of potentially regressive early precancerous lesions.

Recommended start ages vary between 25 and 32 years with the majority of studies coming to the conclusion that 30 years is the best cut off age. The combined follow up of the European RCTs by Ronco showed no protective effect against cervical cancer in women below 30 years at study entry. At the same time, in women of 30-34 years at study entry the effect of HPV based screening on reduced numbers of invasive cancer was substantial with 5/117'345 invasive cancer cases/ person years in the intervention group vs 15/102'598 in the control group.
On the other hand in the ATHENA study 30% of the CIN3+ cases were found in women between 25 and 29 years and more than half of these women had normal cytology. This indicates that advanced precancerous lesions exist in this age group that will go undetected with cytology screening only. Based on these findings one could come to the conclusion that a start age for HPV based screening of 25 years may be better. One possible explanation for this apparent discrepancy for women between 25 and 30 years may be that CIN3+ progression to invasive cancer is slow enough that many of these lesions can be caught at the age of 30 -35.
What is the best strategy for a country may also be related to the age specific cancer incidence rates. E.g. the UK seems to have much higher cervical cancer incidence rates in women of 25-35 years than Switzerland (around 17/100'000 in the UK versus less than 8 in Switzerland in this age group). Therefore in the UK an HPV based screening start age of 25 may be better than 30. Indeed in the UK HTA all HPV based screening strategies start at 25 years [2].
In Switzerland the cervical cancer incidence rate in women below 30 years is low but reaches a first peak in women between 35 and 39 years. Therefore, in Switzerland, it seems prudent to start testing with HPV at the age of 30. This should avoid unnecessary colposcopies and overdetection of regressive early precancerous lesions in women between 20 and 30 years and still allow better prevention of cancer cases in the age group between 30 and 40.

Health economic studies also support this cut off age. Most studies that compared 30 years with younger or older ages came to the conclusion that 30 years is the most cost effective solution.

11.1.3 Research Question 1c: How does the optimal algorithm for first line screening with HPV compare to the current testing with cytological tests in terms of Incremental cost effectiveness ratios (ICERs) of costs per modelled life years gained (LYG) or quality adjusted life years (QALYs)?

Cost effectiveness results consistently show that HPV based screening is either cheaper than cytology based testing or cost effective at ICER rates below acceptability thresholds.

11.1.3.1 Cost effectiveness within country specific studies

The most often analyzed strategy of **HPV with cytology triage** dominated cytology based testing in 9 out of 13 studies. In these cases often no ICERs were shown. In the remaining studies the strategy was more expensive at ICERs below acceptability thresholds.

HPV based screening with partial genotyping and direct referral to colposcopy for HPV16/18 positive women and cytology triage for other hrHPV types, was the most clinically effective solution in all 4 studies that modelled this strategy. It dominated HPV with cytology triage in 2 studies and was more expensive at ICERs below acceptability thresholds in the other 2 studies.

Cotesting was only a cost effective solution in one study. In all other studies it was either dominated or resulted in ICERs above an acceptable threshold.

In conclusion, from a cost effectiveness standpoint HPV with cytology triage and HPV16/18 genotyping strategies seem attractive by being either cheaper than cytology based screening or by being more effective and affordable at ICERs below acceptability thresholds. Cotesting is not an attractive solution from a cost effectiveness standpoint.

11.1.3.2 Transferability of health economic studies to the Swiss health system

In order to assess how the cost effectiveness results might translate into the Swiss situation a transferability analysis was done.

This analysis depends on several assumptions about Swiss reference parameters as described in the methods chapter. The assumptions have a number of limitations.

It has been assumed that Swiss screening follows the recommendations published by the Swiss Society for Gynecology and Obstetrics (“Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe, SGGG”) [53]. It is however probable that these recommendations are not followed completely. Indeed, a recent survey by the Swiss BAG showed that many women are invited far more frequently than recommended for cervical cancer screening by their gynecologist [96].
If a higher frequency for cytology based screening is assumed (e.g. 2 yearly), the cost of current screening in Switzerland would be higher. As 2 yearly cytology based screening was also dominated by HPV based screening strategies [29, 30, 35, 36, 60] the case for a change to HPV based screening would be even more favorable.

HPV prevalence data for Switzerland were taken from only one publication [97] as cited in [62] based on 7’254 women from the cantons of Jura, Neuchâtel and Fribourg tested in 2000-2001. Studies in the UK have found differences of a factor of 2 between HPV

prevalence rates in different cities [62]. It is not known whether similar differences exist between Swiss regions or if the prevalence data assumed as Swiss reference are representative for the whole country.
Compared to other European countries the available Swiss HPV prevalence rates are lower in younger women and higher in older women over 40 years old.
Based on the study of de Kok [80], higher HPV prevalence rates should make cytology based screening more favorable (and vice versa). However, the Australian and UK studies which used the same Markov model for their studies (albeit calibrated to their specific HPV prevalence and cancer incidence rates), come to similar conclusions in terms of clinical and cost effectiveness of different HPV based strategies compared to cytology based strategies even though Australia has lower and the UK higher HPV prevalence rates than Switzerland. Also in Belgium HPV prevalence is higher than in Switzerland but HPV based screening was still more effective and cost effective than cytology based screening [28]. Therefore there is no strong reason that results from other countries may not be transferable due to the described differences in HPV prevalence.

No publications were found on the sensitivity of cytology based screening in Switzerland. This is an important limitation, as the sensitivity is an important influential parameter for the relative clinical and cost effectiveness of cytology or HPV based screening. As an example in the German health economic study, cytology based screening was less effective and cheaper than HPV based screening when sensitivities from international publications were used. On the other hand it was dominated, when the lower sensitivities observed in German studies were modelled [30, 60]. In the absence of data, it was impossible to assess whether the different studies modelled lower or higher sensitivities than representative for Switzerland.
It is important to note that regardless of the sensitivities assumed in the studies all came to the conclusion that cytology based screening was less effective. The differences between studies were rather in the incremental cost effectiveness ratios for the strategies being assessed.

When studies were analyzed against the Swiss reference data, 3 studies were potentially transferable as is [30, 32, 35, 60], 1 study was potentially transferable with an offset (no screening was modelled below 30 years) [28] and 2 studies may become transferable, if Switzerland should decide to switch to an organized screening program [2, 29].
The remaining studies either had insufficient data to decide on transferability or showed relevant differences that indicate no transferability.
The potentially transferable studies recommended either HPV with cytology triage with a 3 to 5 yearly frequency or a HPV 16/18 genotyping strategy with 5-6 yearly frequency.

11.1.3.3 Deduction of cost by adaptation of purchasing power parities

None of the studies provided model results in a way that allowed direct adaptation of the results into Swiss values. Therefore it was only possible to translate values for cost and cost effectiveness ratios into CHF/LYG or /QALY by adaptation to purchasing power parities.

After translation to CHF by adaptation to purchasing power parities for the studies that showed potential transferability, a consistent picture showed with the results from country

specific studies: 5 yearly HPV with cytology triage and HPV with partial genotyping remained cost effective strategies with values below acceptability thresholds.

The costs for cytology and HPV tests were also adapted to CHF by application of purchasing power parities. Current Swiss costs for cytology were within the range that was used in models, which is an important aspect for the plausibility of the transferability.
The costs for HPV tests in the models varied between 20 and 92 CHF. In Switzerland a Tarmed value for HPV testing has yet to be defined for use in primary cervical cancer screening. If the future costs of HPV testing in Switzerland were to be above that range, further analysis would be necessary to verify that the results of the studies can still be considered transferable.

In conclusion, from the wide range of studies with different input parameters and specifically from the studies that showed potential transferability, it is highly likely that in Switzerland HPV based screening will be cost effective with ICERs below 100'000 CHF/LYG or QALY.

Given the large number of health economic studies consistently indicating superior clinical and cost effectiveness of the strategy of 5 yearly HPV with cytology triage, the evidence in favor of this strategy is considered strong. When a decision has to be taken concerning follow up frequencies of women with HPV+/cyt- results, a 12 months interval may be ideal. Shorter intervals of 6 months led to much higher costs while longer intervals of 24 months may involve a higher loss to follow up of affected women [2, 32].

For the strategy involving HPV16/18 genotyping the number of studies is smaller, but results from health economic studies are highly consistent concerning clinical effectiveness. Also all studies found this strategy on the cost effectiveness frontier, albeit at different ICERs. The evidence on this strategy is therefore judged as emerging.
As a side note – HPV16/18 genotyping was described as a highly attractive strategy in vaccinated women. The prevalence of HPV16/18 is much lower in these women than in the general population and the rates of colposcopy / CIN3+ detected become increasingly attractive. In fact in the UK it was assumed that in vaccinated women this strategy will have lower colposcopy rates than current cytology based screening [2]. Therefore this strategy should be considered for implementation in Switzerland in the future.

11.2 Hypothesis 2: HPV based cervical cancer screening is feasible

It is concluded that HPV based cervical cancer screening is feasible. However measures have to be taken to ensure adherence to policy, as suggested in chapter 11.4.

No hard barriers were identified for the implementation of HPV based cervical cancer screening. However, the results of the feasibility analysis show that certain basic conditions should be fulfilled when cervical cancer screening with HPV is implemented. A number of relevant aspects for a successful introduction of HPV based screening are described in chapter 10.

Adherence to policy was identified as the most important aspect. If the HPV test is performed at too young an age or more frequently than necessary, more transient infections

will be identified and more women will be referred unnecessarily to follow up tests and treatment procedures.

Opportunistic screening in Switzerland has been very effective in reducing cervical cancer incidence in Switzerland. However there are indications that women are currently invited more often to screening than recommended [96].
The Belgian HTA showed that stricter control of reimbursement has led to better compliance with reduced screening frequencies in the current cytology based screening program [28]. In Switzerland this would require that stricter controls are done e.g. by the health insurance companies for the reimbursement of screening tests.

Successful implementation in an opportunistic setting requires that the new recommendations are implemented by the most influential stakeholder groups. In Switzerland gynecologists have a strong influence on screening participation by provision of information to women on the topic and sending out invitations. A stakeholder analysis by Altermatt [98] showed that a potential switch from the current cervical cancer screening to HPV based screening with longer screening intervals is perceived as an economic threat to gynecologists in Switzerland. A moral hazard occurs, if the adherence to policy is in conflict with economic interests of the drivers of adherence to policy.

All measures to monitor and drive adherence are more easily set up within an organized screening system, which currently in Switzerland does not exist. Extra costs for the implementation of an organized screening program would occur. On the other hand the benefit of implementing an organized screening system is not only that quality and cost can be better controlled, but also that women may be reached that currently do not attend screening at all. The overall benefit of this may even be higher than that of replacing cytology by HPV as the primary screening test [81].

11.3 Limitations of this study, further research areas

The following limitations apply to this study:

11.3.1 Literature selection and analysis process

In the literature selection process language restrictions were applied. Only English and German language publications were included. In addition only Pubmed and the CRD databases were searched. This may have biased for publications from the US, UK, Australia and Germany, so that the viewpoints from these health systems may be overrepresented in the analyzed literature. Indeed in the literature process one Italian HTA and 2 systematic reviews from France and Spain were identified in local language that were not included in the study.
On the other hand both the US and Germany have opportunistic cervical cancer screening programs and many points raised in these publications are relevant for the Swiss health system. In addition meta analyses independent of a specific health system and health economic studies and HTAs from several other European countries were included so it is assumed that the literature is representative of the current knowledge and opinions on the topic.

No documented quality assessment of systematic reviews and meta analyses was done by application of a checklist. Instead only a sanity check was done that the included

publications fulfilled basic quality criteria such as clear definition of the research question, description of the literature search process, inclusion of recent literature, critical appraisal of the analyzed studies (e.g. risk of bias), and discussion of limitations.
From the sanity check done it seemed that the results of the different publications seem not to correlate with their quality but rather with the date of publication. More recent publications seem to be more favorable for HPV based screening based on the additional data available to them from European RCTs and US cohort studies.

Several systematic reviews exist on the clinical evidence of HPV based cervical cancer screening. However, to the knowledge of the author no similarly comprehensive and detailed systematic review on the health economic evidence on the topic is currently available. Therefore the focus of this study was layed on a structured quality assessment of the health economic evidence by application of the EURONHEED checklist.

11.3.2 Available data on the current Swiss screening execution and effectiveness

As discussed in chapter 11.1.3.2 the transferability analysis is based on only published recommendations for Swiss screening and no analysis of the actual adherence to these recommendations in Switzerland was done. No data on the actual sensitivity of cytology screening in Switzerland were available. HPV prevalence data rely on one publication with data from 3 cantons only. These limitations are relevant and may have biased the results of the current study.
However, based on the wide range of input parameters that were used across the different included studies and the fact that all came to the conclusion that HPV based testing is more clinically effective than cytology based screening, and either cheaper or cost effective with ICERs below acceptability thresholds, it appears likely that these results will apply to the situation in Switzerland as well.
Nevertheless further research is indicated to determine the adherence to recommendations, the sensitivity of cytology based screening in Switzerland and HPV prevalence in women of 30 years and older.

11.3.3 Deduction of cost in CHF

None of the studies provided results in a way that allowed direct adaptation of the results into Swiss values (e.g. by providing cost and units for all aspects). Therefore it was only possible to translate values for cost and cost effectiveness ratios into CHF/LYG or /QALY by adaptation to purchasing power parities.
Even though it is impossible to deduce the true costs for Switzerland by this rather simple transformation, the values in CHF are better able to show where the potential costs in Switzerland might be than the values in the currency of another country and they make values of different studies more easily comparable by using the same currency and cost year.
In order to calculate the true costs for Switzerland a Swiss health economic evaluation should be done. Potentially one of the existing health economic models of another country could be used, and adapted to the Swiss health care system by calibration to Swiss epidemiological data of HPV prevalence and cervical cancer incidence and Swiss costs for screening, diagnosis and treatment.

11.3.4 Self-sampling for HPV based screening

This study was limited to HPV based screening with samples taken by health professionals and did not address self-sampling for HPV based screening.
With this approach sampling, storage and transport of samples are under a comparable level of control as with sampling for cytology based screening. Therefore this approach allowed comparison of the efficacy of cytology versus HPV based screening without introducing additional complexity.
However, with HPV based screening self-sampling by women is possible and was indicated as a way to reach women who currently do not participate in cervical cancer screening for different reasons [28, 29, 49, 67]. Several publications on the topic are available [99-103], but were not analyzed for this thesis. According to Cuzick, self-sampling for an HPV test leads to lower sensitivity than when samples for an HPV test are taken by a health professional, but to higher sensitivity than with a cytological test [49].
The effect of self-sampling on the sensitivity and specificity of HPV based screening should be further analyzed.
This thesis comes to the conclusion that unless self-sampling has comparable sensitivity, the preferred screening involves sampling by health professionals. Self-sampling should be considered for women who otherwise would not attend screening. For this population a test that may be less sensitive would still be more advantageous than no screening at all.

11.3.5 Focus on unvaccinated women

This study focused on the population of unvaccinated women even though primary prevention of cervical cancer involves vaccination of young women before they become sexually active.
In Switzerland, according to a national representative survey of the BAG in 2014, only 41% of the 18-24 year old women had received the necessary 3 vaccination doses against HPV and 47% were not vaccinated at all [96].
Therefore unvaccinated women still represent the majority of women eligible for cervical screening in Switzerland.
In several studies analyzed, strategies for vaccinated women were also discussed. It was indicated that one of the recommended strategies with HPV16/18 genotyping is even more favorable in vaccinated women than in unvaccinated women. Adoption of this strategy may therefore serve both vaccinated and unvaccinated women allowing one algorithm for all women independent of vaccination status. Having one algorithm for all women would reduce complexity and facilitate adherence to recommendations.

Nevertheless a separate study should be done to confirm what the best strategy is for vaccinated women in Switzerland. A list of all model based cervical screening evaluations including vaccinated and unvaccinated populations was published recently by Mendes and could serve as a starting point for this further research [104].

11.3.6 New biomarkers

Finally, the ideal tumor screening marker is 100% sensitive and 100% specific (and does not exist yet). More research is therefore ongoing and results should be closely monitored how the specificity of HPV based screening can be further enhanced.

11.4 Conclusions for potential policy changes for the Swiss screening settings

It is concluded that clinical and health economic evidence strongly supports the recommendation of 5 yearly HPV based screening for women of 30 years and older.
The best algorithms seem to be 5 yearly HPV testing with cytology triage or HPV16/18 genotyping with direct referral to colposcopy for HPV16/18 positive women.
Consideration should be given to offering self-sampling to women who currently do not attend cervical cancer screening.

At the same time it will be important that measures are taken to ensure adherence to policy.

Setting up an organized screening program is the ideal solution, which would also allow systematic evaluation of the clinical and cost effectiveness of cervical cancer screening in combination with the cantonal cancer registries.

Experience in the Swiss Health System shows, that setting up country wide organized screening programs may face political opposition. Centrally organized programs will shift some costs from women and health insurance companies (who will have to pay for fewer screening tests), to cantons, which will have to fund infrastructure for data collection and invitations and reminders. In the light of the effectiveness of the current opportunistic screening in Switzerland, which has among the lowest cervical cancer incidence rates in Europe, it may be difficult to convince political opponents of centrally organized screening programs of the importance and urgency for a change.

Other ideas to ensure adherence to policy should therefore be explored during the absence of an organized screening program. Reimbursement controls are one important element. In addition, in the absence of a central database and full electronic health records, an “electronic screening booklet” could be established analogous to the existing “electronic vaccination booklet” to document screening events and results. This would allow an overview of screening tests and frequencies even when women change gynecologists and / or health insurance companies. It may also provide an opportunity for reminders by mail or SMS with minimal additional infrastructure.

A comprehensive stakeholder analysis for cervical cancer screening in Switzerland is available in the master thesis of Prof. HJ. Altermatt “Strategieoptionen zur Einführung des HPV-Tests in das Vorsorge-Screening für Gebärmutterhalskrebs in der Schweiz“ [98].
The thesis of Altermatt shows that the most critical stakeholders may be gynecologists, who may perceive a change in policy to longer screening intervals and particularly to a potential centralization of screening as an economic threat or an interference in their relationship to their patients.
Measures to ensure support for a policy change by this important stakeholder group may consist of education on current clinical and health economic evidence, involvement in the creation of policy and refraining from centralization of sampling and communication of screening results. Thus, gynecologists would still remain the central contact person for women’s health questions. In addition, should an organized screening program be implemented, this might reach women, who currently do not attend screening at all. Besides better effectiveness of screening in the population of the eligible women, this would provide

additional income for gynecologists and compensate for longer screening intervals in women who attend already now.

Stakeholders that would most benefit from a change are the women. They are currently invited more often than necessary to cervical cancer screening and undergo screening with a test that does not lead to the best possible clinical effectiveness. As the majority of screening occurs in healthy women, screening tests are often paid out of pocket as part of the health insurance franchise. In addition, taking a cervical smear is often considered as unpleasant. Information that a negative HPV test will allow fewer screening events and greater security against cervical cancer may therefore create a strong demand by this stakeholder group.

It is concluded that the evidence in favor of HPV based cervical cancer screening is strong enough to challenge the current clinical effectiveness, cost effectiveness and suitability of the cytology based screening approach in Switzerland. In line with the regulations of the federal law for health insurance a reassessment of the current reimbursed strategy should therefore be done e.g. as part of the new HTA process by the BAG.

It is hoped that the data and references provided by this study will be helpful as input for this HTA process.

Martina Hahn, Zug, July 2016

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13 Appendix 1: "Literature search algorithms"

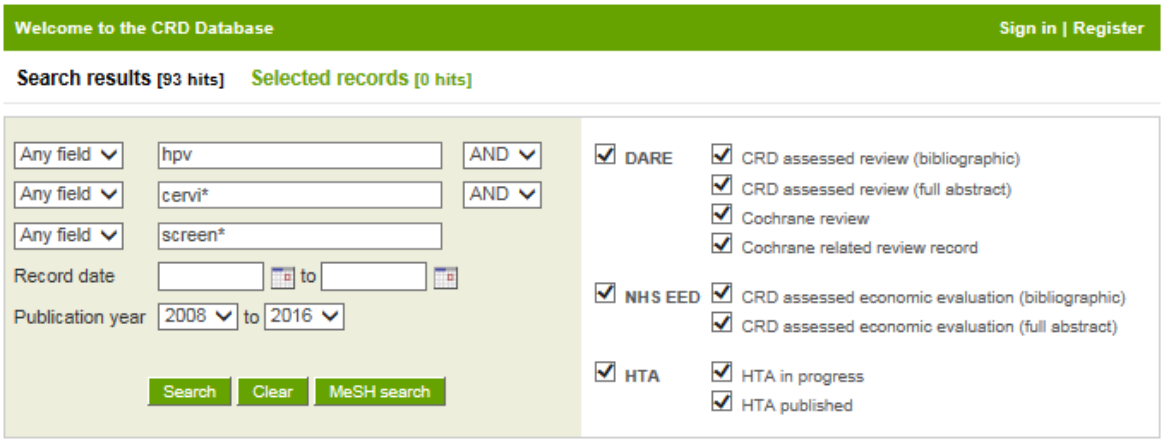
13.1 Search algorithm for Clinical Systematic Reviews and Meta-analyses in PubMed

Search
((((((((((("Papanicolaou Test"[Mesh]) OR "Cytological Techniques"[Mesh]) OR liquid cytology) OR cytology) OR pap test) OR pap screening))
AND ((((((((((("Atypical Squamous Cells of the Cervix"[Mesh]) OR "Squamous Intraepithelial Lesions of the Cervix"[Mesh]) OR "Uterine Cervical Dysplasia"[Mesh]) OR "Cervical Intraepithelial Neoplasia"[Mesh]) OR "Uterine Cervical Neoplasms"[Mesh])))) OR cervix cancer))
AND ((("Early Detection of Cancer"[Mesh]) OR screening) OR screen*))
AND ((((((("DNA Probes, HPV"[Mesh]) OR "Papillomaviridae"[Mesh]) OR "Human Papillomavirus DNA Tests"[Mesh])))) OR (((HPV) OR Human Papillomavirus) OR Human Papilloma Virus)))
AND ("2008/01/01"[Date – Publication] : "3000"[Date – Publication]))))))))
Filters: Meta-Analysis; Systematic Reviews

Output March 12, 2016: 123 records

13.2 Search algorithm for Clinical Systematic Reviews, Meta-analyses, HTAs and Health economic Studies in CRD Databases

http://www.crd.york.ac.uk/CRDWeb/



Results for: ((hpv) AND (cervi*) AND (screen*)) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 2008 TO 2016

Output March 12, 2016: 93 records

13.3 Search algorithm for HTAs, Health economic Studies and Evidence-Based Medicine Publications in PubMed

(((((((“Papanicolaou Test”[Mesh]) OR “Cytological Techniques”[Mesh]) OR liquid cytology) OR cytology) OR pap test) OR pap screening))
AND ((((((((((((“Atypical Squamous Cells of the Cervix”[Mesh]) OR “Squamous Intraepithelial Lesions of the Cervix”[Mesh]) OR “Uterine Cervical Dysplasia”[Mesh]) OR “Cervical Intraepithelial Neoplasia”[Mesh]) OR “Uterine Cervical Neoplasms”[Mesh])))) OR cervix cancer))
AND (((“Early Detection of Cancer”[Mesh]) OR screening) OR screen*))
AND ((((((“DNA Probes, HPV”[Mesh]) OR “Papillomaviridae”[Mesh]) OR “Human Papillomavirus DNA Tests”[Mesh])))) OR (((HPV) OR Human Papillomavirus) OR Human Papilloma Virus)))
AND (((((((((“Models, Economic”[Mesh]) OR “Models, Econometric”[Mesh]) OR “Economics”[Mesh]) OR “Evidence-Based Medicine”[Mesh]) OR “Cost-Benefit Analysis”[Mesh]) OR “Markov Chains”[Mesh])))) OR ((((((health technology assessment) OR ebm) OR evidence based medicine) OR economic evaluation) OR comparative effectiveness research) OR Cost effectiveness)))
AND (“2008/01/01”[Date – Publication] : “3000”[Date – Publication]))

Output March 12, 2016: 238 records

14 Appendix 2: "Description of Randomized Controlled Trials and Cohort Studies"

Table 8: Description of Randomized Controlled Trials and Cohort Studies

Study	Age Size	Intervention and Comparator	Colposcopy threshold	Most important results
RCTs				
POBASCAM Netherlands [16] [17] (intermediate report)	29-56 I=19'999 C=20'106	Round 1 I= HPV+cyt C= cyt Round 2 after 5 years: HPV+cyt for both arms	Cytology findings of HSIL or worse or repeated ASC-US or persistently HPV pos after 18 months	In the first round of screening there was a non-significantly higher relative detection rate of cancers and CIN3+ and a significantly higher detection rate of CIN2+ In the 2nd screen after 2 years there was a significant reduction of cervical cancer and CIN3+ and a non-significant reduction of CIN2+ Over both screening rounds cancer detection rates were non-significantly reduced, CIN3+ about the same in both arms and CIN2+ detection was non-significantly augmented. Relative detection of CIN3+ in round 1 for I vs C= 1.15 (0.92-1.43) Relative detection of CIN3+ in round 2 for I vs C= 0.73 (0.55-0.96) Relative detection of CIN3+ over both rounds for I vs C= 0.96 (0.81-1.14) Relative detection of CIN2+ in round 1 for I vs C= 1.25 (1.05-1.50) Relative detection of CIN2+ in round 2 for I vs C= 0.88 (0.71-1.08) Relative detection of CIN2+ over both rounds for I vs C= 1.08 (0.94-1.24) There were no significant differences between age groups of 29-33 vs 34-56 The authors conclude that HPV testing should be implemented in the Dutch screening system starting at the age of 30 years

Study	Age Size	Intervention and Comparator	Colposcopy threshold	Most important results
ARTISTIC England [4] [27]	20-64 I=18'386 C=6'124	I=HPV+LBC C= LBC (+HPV measured, but masked from patients and investigator and not taken for treatment) 2 rounds of screening 3 years HPV + LBC for all	Cytology findings of HSIL or worse or if two consecutive LSIL or three consecutive ASC-US or persistently HPV pos after 12 -18 months	Relative detection of CIN3+ in round 1 for I vs C= 0.97 (0.75-1.25) Relative detection of CIN3+ in round 2 for I vs C= 0.53 (0.30-0.96) Relative detection of CIN3+ over both rounds for I vs C= 0.85 (0.67-1.08) Relative detection of CIN2+ in round 1 for I vs C= 1.14 (0.94-1.38) Relative detection of CIN2+ in round 2 for I vs C= 0.63 (0.42-0.96) Relative detection of CIN2+ over both rounds for I vs C= 0.99 (0.83-1.19) Different from other studies ARTISTIC did not detect more CIN3+ in round 1 with HPV based testing. However consistent with other studies in round 2 CIN3+ rates were significantly reduced with HPV based testing and over both rounds there was no significant difference between intervention and control group. This study suffered from a comparatively high loss of follow up as less than 70% of the women participating in round 1 complied with rescreening within the timeframe of the study Round 2 was therefore excluded from the analysis of the systematic review of the German IQWiG The systematic review of Arbyn 2012 excluded the ARTISTIC study round 1 from meta-analysis. They assume that this study used a comparatively low threshold of considering LBC samples as positive leading to abnormal cytology rates of up to 17%.

Study	Age Size	Intervention and Comparator	Colposcopy threshold	Most important results
Swedescreen Sweden [18], calculation of sensitivities and PPV of different screening strategies based on [19]	32-38 I=6257 C=6270	I= cyt + HPV C= cyt	C= ASC-US or worse (in Stockholm) or Pap retesting with ASC-US or CIN1 (other cities) I=cyt pos as above, if cyt normal and HPV pos: retest after 12 m, colposcopy if either cyt positive or HPV type persistently positive	Authors conclude in [19] that HPV testing is more sensitive than cytology testing to detect CIN2+ which can be treated as precursors of cervical cancer and lead to reduced incidence of CIN3+ in subsequent screening rounds. There seems to be some overdiagnosis of CIN2 as the combined detection of CIN2 over both round 1 and 2 was higher in the intervention group than the control group. CIN3+ / CIN2+ / CIN2 Round 1: 1.31 (0.92-1.87) / 1.51 (1.13-2.02) / 2.01 (1.19-3.40) Round 2: 0.53 (0.29-0.98) / 0.58 (0.36-0.96) / 0.85 (0.38-1.90) A strength of this study is that CIN2, CIN3 and cancer cases were taken from cancer registries and not only collected through study data. Results were calculated on an intention to treat basis and protocol violations were not excluded from the analysis, so that they potentially represent a real life screening setting. In [18] the authors compare different potential screening strategies based on the data (including HPV subtyping) from women in the intervention arm. They conclude that sensitivity of detection of CIN2+ or CIN3+ is only increased compared to cytological testing if all hrHPV subtypes are followed up with retesting. Cotesting with both cytology and HPV did not significantly increase sensitivity, but had lower PPV than HPV testing followed by cytology triage and retesting for cytology negative women. The authors also calculated that cotesting resulted in 105% more screening tests performed, while HPV testing with cytology triage only increased the number of screening tests by 12%. Relative sensitivity for CIN3+, CIN2+ and relative PPV compared to cytology only: CIN3+ / PPV Cotesting of HPV with cytology: 1.40 (1.23-1.60) / 0.43 (0.33-0.56) HPV with cytology triage and retesting after 12 months: 1.34 (1.16-1.54) / 0.90 (0.70-1.16) CIN2+ / PPV Cotesting of HPV with cytology: 1.35 (1.15-1.60) / 0.42 (0.28-0.61) HPV with cytology triage and retesting after 12 months: 1.30 (1.09-1.54) / 0.87 (0.60-1.26)

Study	Age Size	Intervention and Comparator	Colposcopy threshold	Most important results
NTCC 1 and 2	General conclusion of the authors after 2 screening rounds: HPV testing protects against the development of invasive cancers HPV testing in women between 25-34 leads to overdetection of regressive lesions In women between 35-60 years the data support the use of stand-alone HPV testing as the primary screening test. Cytology triage is recommended before colposcopy to increase PPV and reduce the number of unnecessary colposcopies. The addition of LBC to HPV testing in primary screening does not improve sensitivity but reduces PPV. Results over 2 screening rounds [12] Number of invasive cancers for older women Pooled results of NTCC1 and NTCC2 showed a reduced number of invasive cancers Round 1 I=6, C=8 Round 2 I=0, C=7 Over both rounds I=6, C=15			

Study	Age Size	Intervention and Comparator	Colposcopy threshold	Most important results
NTCC 1 Italy Younger women [12] [14]	25-34 years I=6002 C=5808	NTCC1: Round 1 HPV+LBC vs. Pap Round 2 : Pap Interval 3 years	C= ASC-US or worse (7 centers) or Repeat cytology with ASC-US and colposcopy with LSIL or worse (2 centers) I=retest after 12 m, colposcopy if either test was positive	The authors conclude that “HPV testing in younger women results in overdiagnosis of regressive CIN2” In focus were: Sensitivity and positive predictive value for CIN2+ (some data on CIN3+). In addition from the data obtained the theoretical sensitivity and PPV of other screening algorithms were calculated Authors conclude from **results after recruitment** [14] that Sensitivity was increased for the detection of CIN2+ (relative sensitivity 1.61 (1.05-2.48)) but not for CIN3+ (0.70 (0.37-1.34)), while relative PPV was lower in the experimental arm for both CIN2+ (0.55 (0.37-0.82)) and CIN3+ (0.24 (0.13-0.45)) On cotesting vs HPV testing alone: “Adding LBC to HPV testing had a negligible effect on sensitivity but strongly reduced PPV compared with HPV screening alone. Therefore HPV testing alone as primary test, with triage of HPV-positive women by cytology seems to be the most reasonable approach” On refining the HPV test: improvements of PPV can be obtained with minimum loss in sensitivity by use of a cutoff of 2pg/ml On feasibility: “We had some difficulty in compliance to repeat testing. Only 70% of women returned for a repeat test despite intensive reminders, which reduced the recorded gain in sensitivity by HPV testing compared with the potential gain.” Results reported after Round 2 [12] Results on round 2 were not reported as CIN3+ but CIN3 or AIS without invasive cancers. Relative detection of CIN3 or AIS CIN2 Round 1: 0.93 (0.52-1.64) 4.09 (2.24-7.48) Round 2: 1.34 (0.46-3.84) 0.43 (0.11-1.66) Over both rounds: 0.99 (0.61-1.65) 2.81 (1.69-4.66)

Study	Age Size	Intervention and Comparator	Colposcopy threshold	Most important results
NTCC 1 Italy Older women [12] [15]	35-60 years I=16706 C=16658	NTCC 1: Round 1 HPV+LBC vs. Pap Round 2 : Pap Interval 3 years	C= ASC-US or worse (7 centers) or repeat cytology with ASC-US and colposcopy with LSIL or worse (2 centers) I=HPV pos ASC-US or worse	In focus were: Sensitivity and positive predictive value for CIN2+ (some data on CIN3+ and invasive cancer) In addition from the data obtained the theoretical sensitivity and PPV of other screening algorithms were calculated Authors conclude from results after recruitment (2006-2) that Sensitivity was increased for the detection of CIN2+ (relative sensitivity 1.47 (1.03-2.09)) but not for CIN3+ (1.25 (0.78-2.01)), while relative PPV was lower in the experimental arm for both CIN2+ (0.40 (0.23-0.66)) and CIN3+ (0.34 (0.21-0.54)) On cotesting vs HPV testing alone: With HPV testing alone the gain in sensitivity compared with the comparator group was similar (for CIN2+ 1.43 (1.00-2.04) for CIN3+ 1.22 (0.76-1.96) but relative PPV improved (for CIN2+ 0.58 (0.33-0.98) and CIN3+ 0.50 (0.32-0.79) On refining the HPV test: Setting the cutoff to 2pg/ml instead of 1pg/ml results in similar relative sensitivity (CIN2+ 1.41 (0.98-2.01 and CIN3+ 1.19 (0.74-1.92)) and yet improved PPV (CIN2+ 0.75 (0.45-1.27) and CIN3+ 0.63 (0.40-1.00)) Round 2 Number of invasive cancers Pooled results of NTCC1 and NTCC2 showed a reduced number of invasive cancers Round 1 I=6, C=8 Round 2 I=0, C=7 Over both rounds I=6, C=15 Results on round 2 were not reported as CIN3+ but as CIN3 or AIS Relative detection of CIN3or AIS CIN2 Round 1: 1.85 (1.16-2.95) 2.07 (1.32-3.24) Round 2: 0.72 (0.23-2.28) 0.76 (0.26-2.19) Over both rounds: 1.61 (1.05-2.47) 1.77 (1.18-2.67) The authors comment that the increase of CIN2 and CIN3 over both rounds can either reflect overdetection of regressive lesions or the lead time gain of HPV testing. In the latter case the control group might have much higher CIN2 or CIN3 cases in a later screening round.

Study	Age Size	Intervention and Comparator	Colposcopy threshold	Most important results
NTCC 2 Italy [12] [13]	25-60 years (separate analysis for 25-34 and 35-60 years) I=24'535 C=24'661	NTCC 2: Round 1: HPV vs. Pap Round 2 : Pap Interval 3 years	C= ASC-US or worse (7 centers) or Repeat cytology with ASC-US and colposcopy with LSIL or worse (2 centers) I=HPV pos	Authors conclude from results after recruitment [13] that In women of 35-60 years Relative sensitivity was increased for the detection of both CIN2+ (relative sensitivity 1.92 (1.28-2.87) and for CIN3+ (2.06 (1.16-3.68)), while relative PPV was non significantly lower in the experimental arm for both CIN2+ (0.80 (0.55-1.18)) and CIN3+ (0.86 (0.49-1.52)) In women of 25-34 years Relative sensitivity was increased for the detection of both CIN2+ (relative sensitivity 3.50 (2.11-5.82) and CIN3+ (2.61 (1.21-5.61)), while relative PPV was non significantly lower in the experimental arm for both CIN2+ (0.89 (0.55-1.44)) and CIN3+ (0.66 (0.31-1.40)) Results on round 2 were not reported as CIN3+ but CIN3 or AIS. Older women Relative detection of CIN3 or AIS CIN2 Round 1: 2.40 (1.43-4.05) 1.93 (1.20-3.09) Round 2: 0.30 (0.08-1.11) 0.29 (0.06-1.40) Over both rounds: 1.70 (1.08-2.67) 1.58 (1.02-2.44) The authors comment that the increase of CIN2 and CIN3 over both rounds can either reflect overdetection of regressive lesions or the lead time gain of HPV testing. In the latter case the control group might have much higher CIN2 or CIN3 cases in a later screening round. Younger women Relative detection of CIN3 or AIS CIN2 Round 1: 3.91 (2.02-7.57) 4.96 (2.80-8.79) Round 2: 0.20 (0.04-0.93) 0.64 (0.21-1.95) Over both rounds: 2.14 (1.28-3.59) 3.38 (2.11-5.43) On the right age to start HPV testing: When the results of Phase 1 (calculated sensitivities for HPV testing only) were compared with measured results of Phase 2, there was no significant heterogeneity for women aged 35-60 but significant heterogeneity for women aged 25-34. "Among women aged 25-34 the large relative sensitivity of HPV testing compared with conventional cytology and the difference between relative sensitivity of HPV testing during NTCC phases 1 and 2 suggests that there is frequent regression of CIN2+ that is detected by direct referral of younger HPV positive women to colposcopy. Thus triage test or repeat testing is needed if HPV is to be used for primary testing in this context" After round 2 the authors state that "HPV testing in younger women results in overdiagnosis of regressive CIN2"

Study	Age Size	Intervention and Comparator	Colposcopy threshold	Most important results
Combined follow up of Swedescreen ARTISTIC POBASCAM NTCC [39]	20-64 176'464 persons Median follow up 6.5 years	As described for individual studies	As above	Authors conclude that HPV based screening provides 60-70% greater protection against invasive cervical cancer compared with cytology. They support HPV based screening from age 30 on and recommend screening intervals of 5 years. Even though the interventions differed greatly between the four studies there was a common effect of protection against cervical cancer. Using HPV testing in cervical cancer screening resulted in a significantly lower number of cervical cancers (Rate Ratio = 0.60 (0.40-0.89)), with no significant heterogeneity between studies (p=0.52) HPV testing protects especially better against adenocarcinoma (RR 0.31 (0.14-0.69)), where sensitivity of cytological testing is lower than for squamous-cell carcinoma (RR 0.78 (0.49-1.25)) A negative HPV test had a very high negative predictive value for later occurrence of carcinoma Cumulative Incidence Rate (CIR) of invasive cervical carcinoma per 100'000 women After 3.5 years / after 5.5 years I=HPV negative women: 4.6 (1.1-12.1) / 8.7 (3.3-18.6) C=cytology negative women: 15.4 (7.9-27.0) / 36.0 (23.2-53.5) This means that 5 yearly testing with HPV is more protective than 3 yearly cytological testing On cost and unwanted side effects of HPV screening Even though all HPV based screening algorithms were better than cytology only, the potential burden by unnecessary colposcopies is different between protocols. Number of biopsies taken were compared between studies: The data show that immediate referral to colposcopy (NTCC) leads to doubling of biopsies taken, while strategies relying on retesting of HPV positive, cytology negative women have comparable biopsy rates as in the control group. Rate Ratio for biopsies between Intervention and Control Arm Rate ratio / heterogeneity between studies NTCC: 2.24 (2.09-2.39) POBASCAM: 1.01 (0.94-1.08) Swedescreen: 0.97 (0.87-1.07) ARTISTC: 1.08 (0.97-1.19) Pooled rate ratio (fixed effects): 1.35 (1.30-1.40) p<0.0001 Pooled rate ratio (fixed effects, NTCC excluded): 1.02 (0.97-1.07) p= 0.236 On the age to start screening: Comparison of different age groups revealed that the gain in efficacy with HPV testing is similar at age 30-34 years compared to older women. The authors discuss that a possible explanation is an increased proportion of adenocarcinomas in younger age groups. They therefore recommend starting HPV based testing at the age of 30

Study	Age Size	Intervention and Comparator	Colposcopy threshold	Most important results
FPHT Finland [10] [9] [7] [8]	25-65 Years I=35'837 C=35'500	C=Pap I= HPV test with cytology triage	C and I= ASC-US or worse (or cytological rescreening after 12 months, Colposcopy and biopsy with LSIL Treat-ment threshold CIN1+ (LEEP) After 2006 in women <30 years only CIN2+ treated	[7, 8] Results at round 1: Authors conclude that primary HPV DNA screening with cytology triage is more sensitive than conventional screening (even though CIN3+ detection was not enhanced significantly). In addition they conclude that in women aged 35 or older, primary HPV DNA screening with cytology triage is more specific than cytology only and decreases colposcopy referrals and follow-up tests. [7] Relative detection of CIN3+ (I vs C) All ages (25-65): 1.44 (1.01-2.05) (all invited women = intention to screen) All ages (25-65): 1.77 (1.16-2.74) (those women who really attended screening) [8] The specificity of HPV with cytology triage was equal to that of cytology alone (99.2 vs 99.1% for CIN2+ p=0.13). Test specificity increased with the age of the women being screened. Relative PPVs for HPV testing with cytology triage vs cytology alone were significantly higher for the outcomes CIN1+ and CIN2+ (1.34 (1.04-1.72)) and non-significantly higher for CIN3+ (1.22 (0.78-1.92). Relative PPVs for HPV testing alone vs cytology would have been only 20% of those of conventional screening by cytology. Colposcopy referrals were 1.2% in both screening arms Special aspects of this study The incidence of cancer and precancerous states after initial screening was only obtained through the cancer registries. The advantage of this approach is that also cancer rates in women not attending the study were reported. The disadvantage is that according to the authors opportunistic screening in addition to the official screening is frequently performed in Finland (about the same number of cervical smears are taken opportunistically as in the organized program) and these screening activities are not registered in the cancer registry. [7]). It is therefore unclear, what triggered the detection of cancer and precancerous lesions. In addition there is a delay in registration of CIN detection and cancer. As discussed in [9] "owing to the use of different registries and delays in registration it was not possible to assess whether cervical lesions were diagnosed during intensive screening of the program or diagnosed outside of the program but initiated by the entry screening test result." The most recent publication [10] does not describe results of screening round 2, but number of cancers and CIN3+ detected since round 1 either through additional screening, opportunistic screening or with testing due to symptoms. The results show that incidence of cancer was similar on a low level in both initial screening negative HPV and cytology tested women and overall cumulated incidence of CIN3+ including round 1 was significantly higher with the HPV intervention group. In the systematic reviews and meta-analyses only round 1 results were therefore reported. The Finnish trial had the lowest described treatment threshold with LEEP treatment after CIN1+ findings.

Study	Age Size	Intervention and Comparator	Colposcopy threshold	Most important results
India [70]	30-59 years I1 34'126 I2 32'058 C31'488	I1=HPV test I2=Pap test C= no screening ("standard care")	Only one screening round, colposcopy was done if either HPV or Pap test was positive. Treatment of LSIL+ was done with cryotherapy, conization, LEEP or cancer therapy depending on histological findings	Women were screened once and when positive underwent colposcopy and directed biopsies. Precancerous lesions or cancer were treated. Women were followed up for 4-8 years. One time HPV screening significantly reduced mortality from cervical cancer while one time Pap testing did not Incidence of cervical cancers (rate per 100'000 women) I1 HPV tested 47.4 I2 Pap test 60.7 C unscreened 47.6 Typically with HPV testing fewer cancer cases were at advanced stages than in the control Cervical cancer mortality rate per 100'000 person-year and hazard ratio (95% CI) I1HPV test 34 0.52 (0.33-0.83) I2 Pap test 54 0.89 (0.62-1.27) C unscreened 64 1.00

Study RCTs with only one round/ cross sectional studies	Population Women Age	Intervention and Comparator	Colposcopy threshold	Most important results
CCCaST Cross sectional study Canada [6]	30-69 years Women who presented for screening in an opportunistic setting were randomized to 2 groups 10'154 women	1 round only: HPV plus Pap vs Pap plus HPV Samples taken in different order in the same visit	Pos HPV test Pos cyt test (ASC-US /AGC or worse) Plus a random sample of women with neg tests	Sensitivity and specificity of HPV testing Depending on the definition of a positive colposcopy result in a "conservative" (CIN2+ was only confirmed if also present in LEEP excision sample) or "liberal" way (CIN2+ was confirmed, if so classified by pathologist) the sensitivity and specificity of HPV vs Pap were the following Authors of systematic reviews only used data obtained with the "conservative definition" Sensitivity with conservative definition HPV: 94.6% (84.2-100.0) Pap: 55.4% (33.6-77.2) Specificity with conservative definition HPV: 94.1% (84.2-100.0) Pap: 96.8% (96.3-97.3) Sensitivity with liberal definition HPV: 45.9% (18.9-72.9) Pap: 43.4% (13.2-73.6) Specificity with liberal definition HPV: 94.2% (93.5-94.9) Pap: 96.9% (96.4-97.4) The order of taking a sample for HPV testing or Pap testing does not influence the result

HPV Focal Canada, organized setting [105]	25-65 years C: 6154 LBC I1: 6215 HPV LBC triage I2: 6279 HPV LBC triage	Round 1 LBC at entry and after 2 years		Not used for any quantitative analysis in systematic reviews. Only first round described, expect to complete trial by Dec 2016
Cohort Studies	Population Age	Intervention and Comparator	Colposcopy threshold	Most important results
Kaiser Permanente Cohort Study KPNC USA [11]	≥30 years 331'818 women	All women underwent cotesting as part of the US cervical cancer screening program Retesting was done after 3 years Total follow up: 4-6 years Cumulative incidence rates are described	Cytology LSIL or worse (regardless of HPV) HPV pos and cytology ASC-US HPV negative and cytology ASC-US were retested after 1 year If HPV positive retesting after 1 year, if persistently positive, colposcopy was offered regardless of cytology	Authors conclude that for women aged 30 years and older a single negative test for HPV is sufficient to reassure against cervical cancer over 5 years and that testing for HPV without adjunctive cytology might be sufficiently sensitive for primary screening for cervical cancer 5 year cumulative incidence rates per 100'000 women Cancer HPV negative women: 3.8 HPV and cytology neg: 3.2 Cytology negative: 7.5 Cytology positive findings in HPV negative women do not indicate a substantially increased risk over 5 year to develop CIN3+ (even though the difference is significant): Risk to develop CIN3+ over 5 years HPV negative cytology positive: 0.86% HPV negative cytology negative: 0.16% P=0.004 However cytology positive findings in HPV positive women indicate a greatly and significantly increased risk over 5 years to develop CIN3+: Risk to develop CIN3+ over 5 years HPV positive cytology negative: 5.9% HPV positive cytology positive: 12.1% P<0.0001

Cohort Studies	Population Age	Intervention and Comparator	Colposcopy threshold	Most important results
ATHENA Industry sponsored study to characterize the cobas HPV test (yields separate result for HPV 16, HPV18 or 12 other hrHPV types) [5]	≥25 years 42'209	All women were tested for cytology and HPV at entry. Follow up was 3 years with annual retesting for both cytology and HPV Women with CIN2+ exited the study Colposcopy was offered to all women at the end of the study	Cytology ASC-US or HPV positive A random sample of women negative for both tests obtained colposcopy to determine true sensitivities	The effect of different screening strategies were calculated from the cumulative incidence rates of CIN2+ and CIN3+ in women who were not CIN2+ at baseline Over three years 347 cases of CIN3+ were identified 47.3% occurred in baseline cytology neg women 9.8% occurred in baseline HPV neg women P<0.001 6/8 invasive cancers were identified at baseline 8/8 invasive cancers were HPV positive at baseline 7/8 invasive cancers were cytology positive at baseline 17/20 cases of adenocarcinoma were HPV positive 13/20 cases of adenocarcinoma were cytology positive CIN3+ At baseline in 17.8% of HPV pos women CIN3+ CIR of over three years: 25.2% (21.7-28.7) in HPV16 pos women 5.4% (4.5-6.3) in women HPV pos for other types than HPV16/18 0.3% (0.1-0.7) in HPV neg women 0.8% (0.5-1.1) in cytology neg women 0.3%(0.1-0.6) in HPV and cytology neg women Colposcopies per 1 case of CIN3+ in women ≥ 25 years with cytology 10.8 (9.4-12.6) with cytology for women of 25-29 years and HPV testing for women ≥30 years 12.9 (11.5-14.8) with HPV 12.8 (11.7-14.5) in women ≥30 years with cytology 10.1 (8.6-12.2) with HPV 13.1 (11.5-15.2)

Cohort Studies	Population Age	Intervention and Comparator	Colposcopy threshold	Most important results
VUSA-Screen Netherlands [71]	29-61 years Women within normal Dutch screening program	At entry all women were cotested for cytology and HPV and HPV subtyping was done (n=25'871) A subcohort was formed from all cyt neg HPV pos women who were age matched to 3 cyt neg HPV neg women each (n=1021) Repeat cytology testing was done on HPV pos women at 12 m and cyt and HPV testing done after 24 m for all women (n=3063)	Cytology >BMD or Cytology BMD and HPV pos Cyt -/HPV+ plus	Testing with HPV alone with cytology triage and with genotyping triage allows reduction of risk for CIN3+ sufficiently to not refer directly to colposcopy Starting HPV testing with ≥30 years looks suitable Relative sensitivity for CIN3+ HPV vs cyt = 1.42 (1.19-1.67) Relative specificity for CIN3+ HPV vs cyt = 0.969 (0.966-0.971) Cotesting vs HPV alone with cytology triage for HPV positive: Small, non-significant difference in CIR for CIN3+ within 3 years: Cotesting cyt neg and HPV neg CIR= 0.05% (0.01-0.42) HPV neg CIR= 0.06% (0.02-0.46) HPV subtyping Cyt+ and HPV 16/18+ CIR= 26.1% (21.4-31.4) Cyt+ and other hrHPV types CIR= 6.6% (4.8-9.0) Cyt- and HPV + CIR= 5.22% (3.72-7.91) Cyt- and HPV 16/18+ CIR= 13.0% (7.93-23.6) Cyt- and other hrHPV types + CIR= 2.44% (1.61-5.25) When stratifying HPV pos women with abnormal cytology into 2 age groups (29-33 and ≥34) no risk difference between the older and younger age group was observed for CIN3+ and CIN2+ Potential weaknesses of the study: All probabilities were adjusted for non-attendance of retesting after 12 and 24 months. As women were blinded to their HPV status, only about 60% of cytology negative women attended the retesting at 12 or 24 months. Also no colposcopies were done in women negative for both cytology and HPV to verify the amount of false negative results

15 Appendix 3: "Research Question 1a and b Qualitative results from systematic reviews and meta-analyses"

Table 9: Summary of information on research questions from the clinical systematic reviews and meta-analyses

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
Huh, 2015, USA [64]	This systematic review was performed to provide new interim clinical guidance for the US based on new publications after 2011 The review is based on the most recent publications from the studies ARTISTIC, NTCC, POBASCAM, FPHT, the combined follow up of women from ARTISTIC, NTCC, POBASCAM and Swedescreen [39] and a recent test characterization study for a new HPV DNA test [5].	"hrHPV screening is highly sensitive, but specificity depends on subsequent evaluation strategies and screening frequencies" A modelling study of triage options based on the ATHENA trial showed that "Triaging positive hrHPV tests with genotyping for 16/18 and reflex cytology for women positive for the 12 other hrHPV genotypes achieved an appropriate balance between safety and test utilization." (test utilization includes number of screening tests and number of colposcopies required to detect one case of CIN3+) "A negative HPV test provides greater reassurance of low CIN3+ risk than a negative cytology result"	"Screening should not occur at intervals shorter than 3 years among women with negative screening results." On combined HPV and cytology testing vs HPV testing alone: "These results suggest that primary hrHPV testing with a negative result with a 3-year screening interval is at least as effective as five-year cotesting". "	"Primary hrHPV screening should not be initiated prior to 25 years of age. "

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[46, 65] IQWiG 2011, 2014 Germany	This systematic review was performed by the German "Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen" to provide information for the German Health System It is based on the studies ARTISTIC, POBASCAM, NTCC 1 and 2, FPHT, Swedescreen , CCCaST and "India"	Results of the studies indicate that HPV testing alone or in combination with cytology leads to lower incidences of CIN3+ and invasive cervical cancer. However these reviews come to the conclusion that no recommendation can be made yet for a specific screening strategy as the available data are incomplete regarding the patient-relevant endpoint of cervical cancer related mortality. In addition is was not possible to compare harms of HPV based screening alone or in combination with cytology compared to cytology alone. Transferability of study findings to the German setting was questioned, as screening strategies in the randomized controlled trials are different from current clinical practice. E.g. CIN2 was often treated in the studies, while in Germany this histological finding will rather lead to intense surveillance.	Not analyzed	Not addressed

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[47] Pileggi, 2014	The goal of this study was to characterize relative detection, relative specificity and relative positive predictive value (PPV) of HPV DNA testing compared to cytology. This meta-analysis is based on the randomized controlled trials ARTISTIC, POBASCAM, NTCC 1 and 2, FPHT, Swedescreen , CCCaST and "India"	According to this study: Relative detection of CIN2+ and CIN3+ is significantly higher with HPV testing than with cytology testing. Specificity was based on availability of colposcopy data and is therefore based on NTCC 1 and 2, FTPH, ARTISTIC and Swedescreen only Specificity over all age groups is higher with cytology testing than with HPV testing. However for women ≥ 30 years the specificity of HPV testing and cytology testing was similar. PPV was not significantly lower with HPV testing than with cytology	"The high sensitivity of HPV DNA testing could only marginally improve by systematically adding the cytology test with an irrelevant increase of precancerous lesions detected "	"Primary screening of cervical cancer by HPV DNA testing appears to offer the right balance between maximum detection of CIN2+ and adequate specificity, if performed in the age group ≥ 30 years."
[44] Arbyn 2012	The goal of the study was to inform clinicians about recent meta-analyses and systematic reviews on 3 possible clinical applications (HPV) testing: including as a primary cervical cancer screening test. This systematic review is based on cross sectional, cohort and test characterization studies, as well as the RCTs ARTISTIC, NTCC, Swedescreen , POBASCAM, FPHT	"Primary screening for hrHPV generally detects more CIN2, CIN3 or cancer compared to cytology at cut-off ASC-US or LSIL, but is less specific." "The loss in specificity associated with primary HPV-based screening can be compensated by appropriate algorithms involving reflex cytology and/or HPV genotyping for HPV16 or 18."	"Combined HPV and cytology screening provides a further small gain in sensitivity at the expense of a considerable loss in specificity if positive by either test is referred to colposcopy, in comparison with HPV testing only." "Randomized trials and follow-up of cohort studies consistently demonstrate a significantly lower cumulative incidence of CIN3+ and even of cancer, in women aged 30 years or older, who were at enrollment hrHPV DNA negative compared to those who were cytologically negative. The difference in cumulative risk of CIN3+ or cancer for double negative (cytology & HPV) versus only HPV-negative women is small."	"There exists a substantial evidence base to support that HPV testing is advantageous … in primary screening of women aged 30 years or older. "

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[66] Patanwala 2013	The objective of this study was to assess the sensitivity and specificity of HPV testing for cervical cancer screening in randomized trials. This systematic review is based on the RCTs ARTISTIC, NTCC, Swedescreen, POBASCAM, FPHT and the study "India"	Authors come to the conclusion that : "This systematic review indicates that after 2 rounds of screening, HPV-testing based screening strategies are more sensitive than cytology for the detection of CIN3 or greater only when referral to colposcopy follows a single positive HPV test. This strategy results in more colposcopies needed to detect a single case of CIN3 or greater or cancer, especially in women over 35 years of age. Because CIN3 and cervical cancer are rare in well screened populations, the impact on increased disease detection needs to be balanced with the impact on cost, numbers of colposcopies, and morbidity associated with potential overtreatment." Sensitivity over 2 screening rounds in this case is interpreted as increased cumulated detection of CIN2+ or CIN3+ over both screening rounds. This interpretation is in contrast to other systematic reviews, where the increased cumulative detection of CIN over 2 rounds is rather taken as a potential indicator of over-diagnosis of regressive lesions. Patanwala also tried to calculate colposcopy rates for all studies and found that colposcopy rates in round 1 per CIN3+ case detected was significantly (p=0.04) elevated in NTCC1 (even though SD-bars of confidence intervals in the graph overlap) and in ARTISTIC (5.4 colposcopies in the intervention arm, 4 in the control arm p<0.01) while in the other studies colposcopy rates were non significantly higher in the control arm	Not addressed	Not addressed

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[67] Saslow 2012 USA	This publication represents US screening guidelines based on systematic reviews of RCTs and cohort studies	For women aged 30-65 years, evidence was found strong to recommend either cotesting with HPV and cytology every 5 years (preferred) or cytology alone every 3 years. Addition of HPV testing to cytology enhances detection of adenocarcinoma of the cervix and its precursors as cytological screening seems to be especially ineffective to protect against adenocarcinoma. Screening with HPV at intervals less than 3 years leads to unnecessary procedures and to potentially harmful treatment of regressive lesions. Cotesting with HPV is more sensitive for CIN3+ than cytology alone and a negative HPV test has a substantially lower subsequent risk of CIN3+ than a negative cytology test. HPV testing in RCTs was often associated with increased colposcopy rates, which can be minimized by extending the interval of screening.	Based on the studies available at this point in time working group 6 on future strategies came to the conclusion (even though as a weak recommendation) that the evidence for the effectiveness of screening based on HPV DNA testing alone is still too preliminary to recommend hrHPV testing alone in the general population: “in most clinical settings in the US, we recommend against the use of hrHPV testing as a primary screening strategy (even with defined follow up triage)” based on the rational that the available data on specificity and relative harms associated with this strategy are of low quality.” “Data are limited to women over the age of 30 years and are derived primarily from studies conducted outside of the United States. HPV-based screening approaches may be most appropriate for countries with organized screening programs where women are invited periodically for screening and referred to specialized centers for evaluation, management, and treatment. “Screening intervals may be extended to 5 years if HPV testing is used for primary screening among women ages 30 and older, when the HPV test results are negative”	There is insufficient data to conclude if the currently recommended cutoff age of 30 for cotesting might be decreased

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[54] Massad 2013 USA	This publication represents US guidelines for the management of abnormal cervical cancer screening tests and cancer precursors based on systematic reviews of RCTs and the Kaiser Permanente cohort studies (KPNC) [11, 72] It makes reference to [67] The strength of this publication is the discussion of risk based approaches for screening frequency and treatment of screening positive women	As screening strategies do not only depend on the primary screening test, but also on the regime of follow up, a risk based approach for women with positive primary screening tests was developed. Immediate colposcopy was recommended when the 5-year risk of CIN3+ exceeds 5%, a 6- months to 12-month return for risk of 2-5%, a 3 year return for risk of 0.1-2%, and a 5-year return interval for risk comparable to co-testing in women with negative primary screening tests or a risk of 0.1% Based on this approach the preferred primary screening for women of 30 - 64 years is cotesting every 5 years with HPV and cytology. Cytology positive women should be treated as per previous guidelines. The fraction of cytology positive HPV negative women was considered so low, that no differentiation of treatment of HPV positive and negative women was deemed necessary. HPV positive, cytology negative women should receive repeat co-testing after 1 year. If HPV test is persistently positive after 1 year or cytology is ASC-US or worse, colposcopy is recommended. If HPV test is negative after 1 year and cytology is negative too, repeat co-testing after 3 years is recommended. HPV genotyping was found an acceptable method. For women with HPV 16 or HPV 18 positive tests immediate colposcopy instead of repeat testing after one year is recommended	HPV testing only was not considered However implicitly the recommendations in this publication say that if HPV testing only would be applied, HPV positive women should receive always cytology triage instead of immediate colposcopy and possibly HPV subtyping for HPV 16 and 18.	Cotesting is preferred for women of 30 years and older For younger women cytology alone should be done

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[56] ACOG, 2012 USA	The goal of this study is to provide clinical management guidelines for screening for cervical cancer The methods of extracting the literature are not described. Included studies are RCTs with cotesting of HPV and cytology (POBASCAM, Swedescreen, NTCC, The Cohort Study KPNC and Modelling done by the US Agency for Healthcare Research and Quality and a European Cohort Study from 2008 [83]	The authors state that in women aged 30-65 years cotesting every 5 years achieves slightly lower cancer rates compared to cytology testing every three years, with less screening and fewer follow-up colposcopy procedures. This is based on a probabilities of CIN3+ development in a European cohort study [83], the KPNC cohort study [11], results of RCTs (POBASCAM and NTCC showed lower CIN3+ values with HPV based testing in the second screening round [12, 16]) and modelling done by the authors [86]. HPV positive cytology negative women should be managed with repeat cotesting after 12 months and receive colposcopy at that time, if cytology is LSIL or HPV is persistently positive Alternatively HPV positive cytology negative women should undergo HPV type testing and colposcopy should be performed directly if HPV 16 or 18 is found. The rational for cotesting is derived from cohort studies, where most transient infections were cleared after 12 months.	HPV testing alone cannot be recommended until it is clarified how to further evaluate patients with positive HPV results. “With resolution of this important limitation, primary HPV screening may become important in the future, particularly because a recent systematic review and a large population-based observational study [11] both suggest that co-testing may have only marginal benefit when compared with HPV testing alone .”	No HPV testing should be performed as primary screening in women younger than 30 years due to the high frequency of transient infections and the low incidence of cervical cancer in this age group.

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[43] Bouchard-Fortier 2014	A Meta-analysis was done on RCTs comparing cotesting with HPV and cytology versus cytology alone. It is based on the RTCs POBASCAM, ARTISTIC, NTCC1 and Swedescreen	Meta-analysis showed that at baseline screening cotesting was associated with significantly higher detection rate of CIN2+ (RR=)) and non-significantly higher detection rates for CIN3+. The pooled analysis for the second screening round (follow-up) showed that co-testing was significantly associated with a lower detection rate of CIN 2+ and of CIN 3+ lesions The overall detection rate ratio of CIN2+ lesions was not statistically significantly higher with co-testing versus cytology alone and about the same for CIN3+. CIN2+ RR (95% CI) CIN3+ RR (95% CI) Round 1 1.41 (1.12-1.76) 1.15 (0.99-1.33) Round 2 0.77 (0.63-0.93) 0.68 (0.55-0.85) Cumulative 1.19 (0.99-1.46) 0.99 (0.87-1.14) They state that harms from screening could not be analyzed from the RCTs as the data provided from the RCTs are incomplete on the number of unnecessary colposcopies, or the number and types of interventions performed at or after colposcopies They recommend modelling analysis to compare different screening algorithms for potential harms.	Only cotesting was analyzed	Age groups were pooled in the analysis. No separate analysis for younger or older women

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[51] Moyer 2012 USA	The US Preventive Services Task Force (UPSTF) performed a systematic review to update screening guidelines RCTs POBASCAM, NTCC, ARTISTIC and Swedescreen were analyzed and the cohort study KPNC	Cotesting every 5 years offers a comparable balance of benefits and harms as cytology testing every 3 years. They summarize the result of the RCTs as follows: In all 4 trials there were slightly lower rates of CIN3+ detected in the second round of screening and fewer cancer cases in the co-testing group than in the cytology group. Differences were small and not always significant From the KPNC cohort study they note that cumulative 5-year incidence of cervical cancer was lower in the HPV-negative and cytology-negative groups than in the cytology negative group. The authors state that the studies did not allow detailed analysis of harms from screening. They say that in general incorporating HPV testing into primary cervical cancer screening will lead to more positive screening results. Therefore the likelihood of prolonged surveillance (after the age of 65, where otherwise screening would be stopped) and overtreatment may increase. In the US it is expected that 11% of women aged 30-65 years will have a normal cytology test result and a positive HPV test result.	The authors discuss that evidence on the benefits and harms of HPV testing alone is limited. However “an emerging chain of evidence suggests that HPV testing followed by cytology in women with positive HPV test results may also be a reasonable screening strategy.”	Women younger than 30 years should be tested with cytology only

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[48] Rebolj 2012	This systematic review aims at the determination of specificity of HPV testing vs cytology in different age groups and is based on the studies NTCC1 and 2, ARTISTIC, Swedescreen, POBASCAM, FPHT, CCCaST and "India"	Besides analyzing the relative detection of CIN1 and CIN2, which are precancerous lesions that often regress, Rebolj analyses how many women will be diagnosed with a "false positive" screening result from their primary cervical screening test, if this test is HPV vs cytology. The authors defined excess detection of CIN2 (compared with cytology screening) as an adverse effect of HPV testing, as CIN2 is often treated, even though many CIN2 lesions will regress. "Adverse screening effects (detection of CIN2) were less common among women aged at least 30 years than among younger women. However, in older women HPV testing still led to more CIN1/CIN2 diagnoses and false-positive tests than cytology." The authors state that this was seen in some RCTs, but not all (ARTISTIC and FPHT), due to the low cytology thresholds applied in the latter studies They cited data from NTCC (with immediate colposcopy after a positive HPV result) where 17 extra CIN2 versus 9 extra CIN3 cases were treated for each extra prevented cancer case [12, 106], indicating an increased burden of CIN2 overdiagnosis by switching from cytology to HPV testing" However they also state that longer screening intervals permitted with HPV testing (based on [79, 83]) may partially compensate the false positive result rate during a woman's life time. With the definition used in this study the frequency of "false positive" tests is increased at all ages. The authors recommend that triage should be added to HPV testing to define a "positive" test result. No colposcopy referral should be done solely based on an HPV positive test result.	Not addressed	The effect of elevated detection of CIN1 and CIN2 was less prominent with women aged at least 30 years than among younger women.

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[45] Murphy 2012	This systematic review aims to assess whether the increase in baseline detection with HPV testing in RCTs corresponds to lower rates in subsequent screening rounds and is based on the studies NTCC1 and 2, ARTISTIC, Swedescreen, POBASCAM, FPHT, CCCaST and "India"	"Across studies, HPV testing was more accurate than conventional cytology and detected significantly more CIN3+ in the first screening round (Mantel-Haenszel [M-H] risk ratio 1.67; 95% CI 1.27 to 2.19) and significantly less in the second screening round (M-H RR 0.49; 95% CI 0.37 to 0.66). There were no differences in pooled rates of CIN2+ (M-H RR 1.19; 95% CI 0.94 to 1.50) and CIN3+ (M-H RR 1.09; 95% CI 0.84 to 1.42), but there was a higher pooled rate of CIN2 (M-H RR 1.37; 95% CI 1.12 to 1.68) over two screening rounds. A trend towards lower rates of invasive cervical cancer was observed." "Colposcopy rates were generally higher with HPV testing at baseline screening and among younger women, reflecting higher detection rates among these groups. The variety of different management strategies resulted in referral rates ranging from 1.1% for women aged 30 to 69 who underwent primary HPV testing (referral threshold of 1 pg/mL) with cytology triage of positive results (referral threshold of ASC-US)(C1), to 13.0% for women aged 25 to 34 who were directly referred to colposcopy after a positive HPV test (referral threshold of 1 pg/mL)"	Not in focus	Additional results from the NTCC trial …indicate that for the 25 to 34 age group, detection of CIN2 was more than four times higher (RDR = 4.54; 95% CI 3.00 to 6.88) for the intervention group (i.e., comparing co-testing to cytology testing alone), and CIN2+ detection was over three times higher (RDR = 3.03; 95% CI 2.28 to 4.03).

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[68] Whitlock 2011 USA	This systematic review was done 2011 for the US preventive services task force and is based on the RCTs ARTISTIC, POBASCAM, Swedescreen, FPHT, NTCC and CCCaST	"Six fair- to good-quality diagnostic accuracy studies showed that 1-time HPV screening was more sensitive than cytology for detecting CIN3+/CIN2+ but was less specific. On the basis of 2 fair- to good-quality randomized, controlled trials (RCTs) (120 533 participants), primary HPV screening detected more cases of CIN3 or cancer in women older than 30 years. Four fair - to good-quality diagnostic accuracy studies and 4 fair- to good-quality RCTs showed mixed results of cotesting (HPV plus cytology) in women aged 30 years or older compared with cytology alone, with no clear advantage over primary HPV screening. Incomplete reporting of results for all screening rounds, including detection of disease and colposcopies, limits our ability to determine the net benefit of HPV-enhanced testing strategies."	"On the basis of indirect comparisons between NTCC phases 1 and 2 cotesting offers no additional CIN3+ detection above HPV screening alone, but may yield more false-positive results"	This review only analyses the benefits and harms of HPV testing for women 30 years and older. No analysis was done for younger women

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[49] Cuzick 2008	A review of meta analyses and systematic reviews on possible clinical applications of HPV testing is provided including the use as a primary cervical cancer screening test. This systematic review is based on early cross sectional studies and the first rounds of RCTs NTCC, POBASCAM and Swedescreen	"Primary screening with Hybrid Capture® 2 (HC2) generally detects more than 90% of all CIN2, CIN3 or cancer cases, and is 25% (95% CI): 15–36%) relatively more sensitive than cytology at a cut-off of abnormal squamous cells of undetermined significance (ASC-US) (or low-grade squamous intraepithelial lesions (LSIL) if ASC-US unavailable), but is 6% (95% CI: 4–7%) relatively less specific." "Basic principles suggest that in such circumstances the more sensitive test should be applied first (i.e., HPV DNA testing) and the more specific test (i.e., cytology) should then be used only for HPV-positive women to determine management." "This approach of using HPV DNA testing as the sole primary screening modality has several advantages: HPV DNA detection assays provide an automated, objective and very sensitive test. This allows for better quality control and reduces the basis for medico-legal claims; (2) cytology can thus be reserved for the 5–15% of women who are HPV-positive. This facilitates high quality cytology and allows the employment of fewer, more focused cyto-screeners; (3) it also avoids the unnecessary triage of HPV-negative ASC-US/LSIL; and (4) a longer screening interval is likely to be safe which would improve both the cost and convenience of screening"	Not addressed	Not addressed

Systematic Review / Meta-analysis	Motivation, included Studies	Research Question 1a: On the clinical effectiveness of HPV testing versus cytology testing	Research Question 1a: Cotesting of HPV with cytology versus HPV testing alone as primary screening test	Research Questions 1b: Age to start HPV testing
[52] Schiffman 2011 USA	"To inform an evidence-based transition to a new public health approach for cervical cancer screening, we summarize HPV natural history and cervical carcinogenicity, review the efficacy of currently available cervical cancer prevention methods, discuss how optimal prevention strategies are guided by HPV biology and technology, and describe important remaining uncertainties and concerns regarding the possible misuse of new screening strategies" This systematic review is based on the RCT studies NTCC, CCCast, Swedescreen, India, POBASCAM, ARTISTIC and cohort studies (especially KPNC)	Now that the sensitivity of HPV tests is beyond question, waiting for results of randomized clinical trials of the various possible HPV screening and management protocols relative to cytology would risk postponing health benefits for many women. Where practical, and following proper regulatory approvals, we advocate implementation of HPV tests as the primary cervical screening test in a well-controlled and evaluable fashion that will allow the best strategies to be sorted out as HPV-based screening (and vaccination) methods continue to improve [e.g. (81,131)]. As we start to use HPV testing for the key function of screening—risk stratification—what we need most is to determine how best to 1) make use of negative HPV tests to lengthen screening intervals substantially and 2) manage women with positive HPV tests while avoiding overtreatment. To save the most lives, HPV testing should be adopted worldwide, especially in low-resource settings where the burden of cervical cancer is the greatest. Now that practical tests are available, the most pressing need is for simple and inexpensive treatments for HPV infections to permit optimal screen-and-treat programs in the poorest places, where women are most threatened by invasive cervical cancer.	"Triage of women who have a positive HPV test with cytology is more economical than cotesting all women with both tests. However, cytology is also an imperfect second test for triaging HPV-positive women; an abnormal cytology finding (especially HSIL) further increases risk (positive predictive value) of CIN3+ among HPV-positive women, but their risk remains substantial after a negative cytology triage result. Therefore, at least in the United States; HPV-positive cytology-negative women require some kind of intensified follow-up before resumption of routine screening"	"Current practice in the United States to restrict carcinogenic HPV testing to women aged 30 years or older, who are past the peak of acute HPV infections, results in a higher positive predictive value of HPV testing because a higher proportion have HPV infections that are persistent."

16 Appendix 4: "Research question 1a-c – Excerpt of answers from HTAs and Health Economic Studies"

Table 10: Extraction of Answers to Research Questions 1a, b and c from Health Economic Studies

<table>
<tr><th>Publication
Year
Country</th><th>Study Description</th><th>Research Question 1a
What test results in the highest clinical effectiveness at the lowest burden of follow up?</th><th>Question 1b
best age to test for HPV?</th><th>Research Question 1c
comparison of (Incremental) cost effectiveness ratios[11]</th></tr>
<tr>
<td>Sroczynski et al.
2010, 2011
Germany
[30, 60]</td>
<td>Goal: Analysis of cost-effectiveness of primary HPV screening for cervical cancer in Germany.
A cohort of unvaccinated women of 15 years until end of life was modelled

Strategies
• Pap test (63% of Pap pos receive repeated Pap test, the rest either HPV testing, cotesting or direct colposcopy)
• Pap + HPV cotesting
• HPV + Pap triage (all HPV positive women receive Pap testing)
• HPV only (43% HPV positive women receive Pap testing, 27% cotesting, 23% directly colposcopy, 3% HPV test repetition, 3% direct therapy)

Frequency: 1-5-yearly intervals for all strategies were modelled
Perspective: 3rd party payer
Results reported in 2007 Euro
Costs and benefits discounted at 3%
Quality score: 0.87
Transferability data score: 0.87</td>
<td>Clinical effectiveness of not dominated strategies shows that primary testing with HPV based strategies is always more effective than testing with cytology of the same frequency.
5-yearly testing with HPV based strategies are slightly more effective than 3 yearly Pap testing

<table>
<tr><th>Strategy</th><th>Discounted effects (LY)</th><th>% reduction lifetime cancer risk</th></tr>
<tr><td>no screening</td><td>28.832</td><td>-</td></tr>
<tr><td>Pap 5y</td><td>28.861</td><td>53%</td></tr>
<tr><td>Pap 3y</td><td>28.869</td><td>70%</td></tr>
<tr><td>HPV 3y</td><td>28.875</td><td>85%</td></tr>
<tr><td>HPV + pap triage 3y</td><td>Not shown</td><td>85%</td></tr>
<tr><td>Cotesting 3y</td><td>Not shown</td><td>85%</td></tr>
<tr><td>HPV 5y</td><td>Not shown</td><td>71%</td></tr>
<tr><td>HPV + pap triage 5y</td><td>Not shown</td><td>72%</td></tr>
<tr><td>Cotesting 5y</td><td>Not shown</td><td>72%</td></tr>
<tr><td>HPV 2y</td><td>28.877</td><td>91%</td></tr>
<tr><td>HPV + Pap-Triage, 2y</td><td>28.877</td><td>92%</td></tr>
<tr><td>HPV 1y</td><td>28.879</td><td>97%</td></tr>
</table>

The burden of screening was not modelled (no numbers of colposcopies were calculated, no QALYs were used).</td>
<td>Not addressed in this study

Based on an earlier German HTA study [107] HPV testing below 30 years is likely to result in increased cost for the health system, due to high prevalence of HPV in younger women. For this reason all models use 2-yearly Pap testing as primary screening test in women <30 years.</td>
<td>3-yearly HPV based testing had an ICER of 9'000 €/Life year gained (LYG) in the base case compared to cytology based testing.
5-yearly testing with HPV based strategies were slightly more effective than 3 yearly Pap testing, however suffered extended dominance from a combination of 3 yearly Pap testing and 3 yearly HPV base testing.

The cost effectiveness of all not dominated strategies is as follows in the base case
<table>
<tr><th>Strategy</th><th>Discounted costs (€)</th><th>ICER (€/LYG)</th></tr>
<tr><td>no screening</td><td>87</td><td>-</td></tr>
<tr><td>Pap 5y</td><td>159</td><td>2'600</td></tr>
<tr><td>Pap 3y</td><td>215</td><td>7'100</td></tr>
<tr><td>HPV 3y</td><td>266</td><td>9'000</td></tr>
<tr><td>HPV 2y</td><td>345</td><td>28'400</td></tr>
<tr><td>HPV + Pap-Triage, 2y</td><td>362</td><td>93'700</td></tr>
<tr><td>HPV 1y</td><td>637</td><td>155'500</td></tr>
</table>

In a scenario, where Pap test sensitivity was lower based on German studies all Pap test based strategies were dominated and
5 yearly HPV based testing was cost effective at 3'700 €/LYG (versus no screening) and
3 yearly HPV based testing was cost effective at 6'100 €/LYG (versus 5 yearly HPV)</td>
</tr>
</table>

[11] ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study.

Publication Year Country	Study Description	Research Question 1a What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to test for HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios[11]
Bistoletti et al. 2008 Sweden [75]	Goal: estimate life expectancy and health care cost per woman of 32 years during their remaining lifetime for 3 screening strategies compared to no screening in Sweden A cohort of unvaccinated women of 32 years until end of life was modelled Strategies • cytology every 3 years for women of 32-50 years and 2 additional cytological tests at ages 55 and 60 • added HPV testing once at age 32 • only 3 screenings with combined cytology and HPV testing at ages 32, 41 and 50 Frequency: as described above Perspective: health care payer Results reported in 2005 US $ Costs and benefits discounted at 0%,3% and 5% Quality score: 0.85 Transferability data score: 0.77 It is important to note that the interventions were not described in detail in terms of follow up on positive primary screening results.	Three screening events at ages 32, 41 and 50 with cytology and HPV cotesting were more effective in terms of life years than 9 screenings with cytology (3-yearly from 32-50, then 5-yearly until age 60). Adding HPV testing once at 32 years had no beneficial effect. Discounted Life years (3%) cytology 29.67 added HPV testing once 29.67 only 3x cotesting 29.69 No data on the potential burden of screening (e.g. number of false positive no results or number of colposcopies were reported) nor were QALYs calculated, as none of the data from the literature was considered sufficiently reliable. However it is likely that with only 3 screenings the burden of screening is lower or at least not higher than with 9 screenings	Not addressed All screening strategies start at 32 years	This 3rd strategy dominated the other two in that it yielded slightly more life years at lower costs. No ICERs were calculated therefore. Discounted costs (3%) cytology 245 added HPV testing once 284 only 3x cotesting 210 health care costs per woman in US $

<table>
<tr><th>Publication
Year
Country</th><th>Study Description</th><th>Research Question 1
What test results in the highest clinical effectiveness at the lowest burden of follow up?</th><th>Question 1b
best age to test for HPV?</th><th>Research Question 1c
comparison of (Incremental) cost effectiveness ratios</th></tr>
<tr>
<td>Kitchener et al.
2014
UK [2]</td>
<td>Goal: Analyze HPV based screening strategies for cervical cancer screening in England

Screening started at 25 years.

Strategies
• (CP) current practice = LBC with HPV triage, 3-yearly from 25-49 years, then 5-yearly
• (S1) HPV with LBC triage
• (S2) HPV with LBC triage (immediate) and HPV 16/18 genotyping (after 24 months) for women who were HPV pos/ cyt neg
• (S3) HPV with HPV 16/18 genotyping
(if HPV 16/18 positive refer to colposcopy, if positive for other hrHPV cytology triage)
• (S4) Cotesting (with HPV 16/18 genotyping after 24 months for women who were HPV pos/cyt neg)

Frequency: for HPV based strategies 5 yearly or 6 yearly or
6 yearly for 25-49 year old women, then 10 yearly
and follow up of positive results after either 24 or 12 months

Perspective: Health system</td>
<td>In general 6-yearly HPV based testing strategies were as effective or more effective in terms of cancer incidence than current cytology based practice, especially if follow up of HPV+/cyt- women was done after 12 months instead of 24 months
The following strategies were more effective than current practice and on the cost effectiveness frontier or give information on screening start age with HPV Cotesting was always dominated in all scenarios.

Strategy coded as follows: Strategy Code, months follow up after negative triage test, age of switch from cytology to HPV based strategy if strategy was not applied from 25 years on. All dominant HPV based strategies had a frequency of 6 yearly

<table>
<tr><th>strategy code</th><th>LY/ woman</th><th>Increase of colposcopies vs CP</th></tr>
<tr><td>S2 24m with 10 yearly frequency for >50years)</td><td>26.2306</td><td></td></tr>
<tr><td>CP</td><td>26.2307</td><td></td></tr>
<tr><td>S1 24m 30y</td><td>26.2308</td><td>1%</td></tr>
<tr><td>S2 24m</td><td>26.2310</td><td>-4%</td></tr>
<tr><td>S2 24m 30y</td><td>26.2310</td><td>10%</td></tr>
<tr><td>S3 24m</td><td>26.2316</td><td>26%</td></tr>
<tr><td>S1 12m</td><td>26.2317</td><td>10%</td></tr>
<tr><td>S2 12m</td><td>26.2320</td><td>26%</td></tr>
<tr><td>S3 12m</td><td>26.2323</td><td>50%</td></tr>
</table>

Life-years were considered as the primary outcome of the analysis. In addition supplementary alternate QALY weights were considered and lifetime risk of cancer was taken as effectiveness measures. Recommendations were made based on the life-</td>
<td>In the base case all strategies are applied starting at age 25.

In additional scenarios younger women received cytology and switched to HPV based testing at age 30 or 35

HPV testing with cytology triage starting at 25 years yielded more life years (26.2317LY) and increased colposcopy rates by 10% compared to current practice (26.2307LY). Switching at 30 or 35 years was as</td>
<td>ICERs were not calculated by the authors compared to current setup as HPV based strategies were more effective and cheaper. However ICERs were calculated for this thesis for the strategies on the cost effectiveness frontier.
Switching from cytology screening to HPV based screening at age 30 was dominated, however is still more effective and cheaper than current practice. Switching at age 30 dominated switching at age 35.
<table>
<tr><th>Strategy code</th><th>Lifetime cost/ woman</th><th>ICER</th></tr>
<tr><td>S2 24m with 10 yearly frequency for >50years)</td><td>131</td><td>baseline</td></tr>
<tr><td>CP</td><td>159</td><td>Dominated</td></tr>
<tr><td>S1 24m 30y</td><td>145</td><td>Dominated</td></tr>
<tr><td>S1 24m 35y</td><td>150</td><td>Dominated</td></tr>
<tr><td>S2 24m 35y</td><td>151</td><td>Dominated</td></tr>
<tr><td>S2 24m</td><td>135</td><td>10’000 (against baseline)</td></tr>
<tr><td>S2 24m 30y</td><td>148</td><td>Dominated</td></tr>
<tr><td>S3 24m</td><td>144</td><td>15’000</td></tr>
<tr><td>S1 12m</td><td>147</td><td>30’000 (dominated, but lower colposcopy rates)</td></tr>
<tr><td>S2 12m</td><td>152</td><td>20’000 (against S3 24m)</td></tr>
<tr><td>S4 12m</td><td>167</td><td>Dominated</td></tr>
<tr><td>S3 12m</td><td>161</td><td>30’000 (against S2 12m)
20’000 (against base line)</td></tr>
</table>
</td>
</tr>
</table>

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to test for HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
	Results reported in 2010 £ Costs and benefits discounted at 3.5% Quality score: 0.86 Transferability data score:0.93	years saved by strategies, rather than based on QALYs, as “the diversity of the findings when different QALY weights are used emphasizes the uncertainty involved in the selection and application of these weightings”	effective as current practice (26.2308LY) at 1% increased colposcopy rate Switch at 35 years had overall higher costs than a switch at 30 years.	

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b What is the best age to start using HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
Huh et al. 2015 USA [37]	Goal: to evaluate the cost effectiveness of cervical cancer primary screening with a HPV-16/18 genotyping test which simultaneously detects 12 other high-risk HPV types. A cohort of unvaccinated women of 30-70 years was modelled Strategies • cytology + HPV triage, • HPV + cytology triage • cotesting • HPV + 16/18 genotyping In the latter strategy women positive for HPV 16 or 18 were directly referred to colposcopy. Women positive for other hrHPV strains were sent to cytology triage. Frequency: 3-yearly intervals for all strategies were chosen Perspective: US health payer Results reported in 2013 US$ Costs and benefits discounted at 3% Quality score: 0.93 Transferability data score: 0.87	HPV testing with HPV16/18 genotyping yielded the most undiscounted Life-years (LY), the most QALYs and the lowest mortality. Strategy LY QALY cytology + HPV triage = 37.978 22.856 HPV + cytology triage = 37.981 22.866 cotesting = 37.982 22.868 HPV + 16/18 genotyping = 37.984 22.874 Burden of screening : HPV testing with genotyping increased colposcopies only slightly compared to cytology with HPV triage and less than HPV testing with cytology triage and cotesting Colposcopies (per 100'000 women annualized) cytology + HPV triage = 2.104 HPV + cytology triage = 2.339 cotesting = 2.967 HPV + 16/18 genotyping = 2.159 HPV testing with genotyping had the lowest number of colposcopies per CIN3+. cytology + HPV triage = 4.76 HPV + cytology triage = 3.95 cotesting = 4.79 HPV + 16/18 genotyping = 3.06 QALYs: Disutilities were assigned to CIN1,2,3 and cervical cancer, however not to screening itself, or being in triage after an initial positive screening test	Not addressed All strategies were applied to women of 30 years and older	HPV testing with HPV16/18 genotyping had an ICER of 7667$ compared to cytology with HPV triage HPV testing with cytology triage and cotesting were dominated by HPV testing with genotyping Discounted Costs ICER US $ $/QALY cytology + HPV triage = 1.230 HPV + cytology triage = 1.749 dominated cotesting = 2.014 dominated HPV + 16/18 genotyping = 1.367 7667

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b What is the best age to start using HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
Arbyn et al. 2015 Belgium [28]	Goal: The analysis of clinical and cost-effectiveness of primary HPV screening for cervical cancer in Belgium. A cohort of unvaccinated women of 30 years until end of life was modelled Strategies • Cytology with HPV triage 3 yearly • HPV with cytology triage 5 yearly (starting with 30 years, in younger women cytology) Frequency: see above, start of screening at age 25 Perspective: 3rd party payer incl. patients out of pocket expenses for health care Results reported in 2014 € Costs discounted at 3% and benefits at 1.5 Quality score: 0.91 Transferability data score: 0.87	5-yearly HPV testing was more effective in preventing cervical cancer cases and gained more life years Different triage options were evaluated and HPV based testing with cytology triage was found to have the best balance between safety and referral rate to colposcopy. **Cervical cancer cases** / **Life years discounted** cytology + HPV triage: 462 / 3'658'751 HPV + cytology triage: 222 / 3'660'369	Not addressed According to literature review and with special reference to the combined follow up by Ronco et al 2013 from 4 big European randomized controlled trials, no protective effect on the reduction of cervical cancer was observed in women younger than 30 years. Therefore a switch to HPV testing at 30 years was chosen.	5-yearly HPV testing was more effective at a lower price than 3-yearly cytology based screening. Base case **Total costs (€)** / **Total costs (€) discounted** cytology + HPV triage: 83'066'833 / 51'786'706 HPV + cytology triage: 68'179'074 / 46'004'382 In a scenario analysis a higher price was assumed for the HPV assay of 58 € instead of 35 € In this case 5-yearly HPV testing was cost effective at a higher price than 3-yearly cytology based screening with an ICER of 4319 €/LYG

<table>
<tr><th>Publication
Year
Country</th><th>Study Description</th><th>Research Question 1
What test results in the highest clinical effectiveness at the lowest burden of follow up?</th><th>Question 1b
best age to start with HPV</th><th>Research Question 1c
comparison of (Incremental) cost effectiveness ratios</th></tr>
<tr>
<td>Accetta et al. 2010
Italy
[76]</td>
<td>Goal: To evaluate the cost-effectiveness of cytology based and HPV based screening algorithms in vaccinated and unvaccinated women in the Italian health system

A cohort of unvaccinated women

Strategies
• Pap test only 3y
• Pap with HPV triage 3y
• HPV with Pap triage 3y
• HPV with Pap triage 5y
• HPV only 3y
• HPV only 5y

Frequency: 3-or 5- yearly
All screening programs start at age 25 and end at age 65

Perspective: health system
Results reported in 2006 €
Costs and benefits discounted at 3%
Quality score: 0.65
Transferability data score: 0.60

Follow up is not well described. I.e. unclear whether HPV only strategies involve direct referral to colposcopies. It is not described, how patients with HPV+/Cyt triage- and Cyt+ (ASC-US)/ HPV triage are followed up.
No sensitivity analysis for unvaccinated women.</td>
<td>Compared to Pap test only or to 3-yearly Pap test with HPV triage (Swiss recommended strategy), HPV based testing with Pap triage was more effective in reducing life time risk of cancer.
3-yearly HPV test only yielded less QALY than HPV with Pap triage while reducing the risk of cancer to the same level.

Therefore HPV testing with Pap triage with a 3 yearly or 5 yearly frequency seems the best strategy.

<table>
<tr><th>Strategies</th><th>reduction cancer risk (%) compared to no screening</th><th>QALY</th></tr>
<tr><td>Pap with HPV triage 3y</td><td>49.5</td><td>29.42803</td></tr>
<tr><td>Pap test only 3y</td><td>52.9</td><td>29.42822</td></tr>
<tr><td>HPV only 5y</td><td>53.7</td><td>29.42958</td></tr>
<tr><td>HPV with Pap triage 5y</td><td>55.0</td><td>29.42991</td></tr>
<tr><td>HPV only 3y</td><td>56.0</td><td>29.43042</td></tr>
<tr><td>HPV with Pap triage 3y</td><td>56.0</td><td>29.43048</td></tr>
</table>

The burden of screening was not addressed. QALYs were used; however no disutilities were assigned to screening itself, being in triage or being treated for CIN.</td>
<td>Not addressed

All strategies are applied starting at 25 years of age</td>
<td>The cost effectiveness plane in the publication mixed strategies with and without vaccination, so the cost effectiveness was calculated for this thesis from the published costs and QALYs (which will introduce some inaccuracy due to taking only the rounded values from the cost and effectiveness tables)

<table>
<tr><th>Strategies</th><th>lifetime cost</th><th>ICER €/QALY</th></tr>
<tr><td>Pap with HPV triage 3y</td><td>149</td><td>dominated</td></tr>
<tr><td>Pap test only 3y</td><td>160</td><td>dominated</td></tr>
<tr><td>HPV only 5y</td><td>176</td><td>dominated</td></tr>
<tr><td>HPV with Pap triage 5y</td><td>136</td><td>4’444</td></tr>
<tr><td>HPV only 3y</td><td>228</td><td>dominated</td></tr>
<tr><td>HPV with Pap triage 3y</td><td>175</td><td>68’421</td></tr>
</table>

HPV with Pap triage every 5 years is more effective and less costly than Pap with HPV triage every 3 years. The ICER to the next less cost effective strategy (Pap test only every 5y) is only 4’444 €/QALY

HPV with Pap triage every 3 years is also on the cost effectiveness frontier, however at a higher ICER of 68’421 €/QALY.</td>
</tr>
</table>

<table>
<tr><th>Publication Year Country</th><th>Study Description</th><th>Research Question 1
What test results in the highest clinical effectiveness at the lowest burden of follow up?</th><th>Question 1b best age to start using HPV?</th><th>Research Question 1c
comparison of (Incremental) cost effectiveness ratios</th></tr>
<tr>
<td>Burger et al. 2012 Norway [32]</td>
<td>Goal: to inform cervical cancer prevention guidelines in Norway.

A cohort of unvaccinated women was modelled

Strategies start at 25 years with 3-yearly cytology with cotesting triage for ASC-US and LSIL or cotesting triage for ASC-US only

switch at 31 years to either
1. No switch cytology 3y
2. HPV with cotesting triage

Frequency: 3/4/5 or 6 yearly (y)
Time to rescreen of HPV+/cyt- women was 6 or 12 months. The number of additional HPV+/cyt- results before referral to colposcopy varied between 1 and 3 (base case)

Perspective: societal (direct medical costs, travel and time of women)
Results reported in 2010US$
Costs and benefits discounted at 4%
Quality score: 0.80
Transferability data score: 0.83</td>
<td>Life Years and lifetime risk of cancer were taken as effectiveness measures.

HPV testing of all frequencies reduced cancer cases more than 3-yearly cytology alone.
HPV based screening yielded more discounted life years when performed at 5 yearly frequencies or more often
Strategies coded by
Primary screening test, yearly frequency, months to rescreen triage negative women

<table>
<tr><th>Primary screening test, post-switch</th><th>Absolute reduction in cancer (%)</th><th>Total discounted life years</th></tr>
<tr><td>no screening</td><td>—</td><td>32.9276</td></tr>
<tr><td>HPV 6y, 12m</td><td>55.59</td><td>32.9500</td></tr>
<tr><td>cytology 3y</td><td>55.45</td><td>32.9502</td></tr>
<tr><td>HPV 5y, 12m</td><td>58.82</td><td>32.9510</td></tr>
<tr><td>HPV 4y, 12m</td><td>63.44</td><td>32.9524</td></tr>
<tr><td>HPV 4y, 6m</td><td>65.26</td><td>32.9529</td></tr>
<tr><td>HPV 3y, 6m</td><td>70.22</td><td>32.9542</td></tr>
<tr><td>HPV 3y, 6m, colposcopy after 1 repeated HPV+/cyt-</td><td>70.49</td><td>32.9543</td></tr>
</table>
</td>
<td>Women were switched to HPV based strategies at either 34 years (base case) or 31 years.

Switching at age 31 dominated switching at age 34.</td>
<td>Cytology with cotesting triage was dominated, while most HPV with cytology triage strategies were on the cost effectiveness frontier, however some with high ICERs
6-yearly HPV will cytology triage is almost as effective as 3-yearly cytology with cotesting triage at a 25% lower price with an ICER against no screening of 29’000 $/LY.
Other HPV based strategies were more effective than cytology based screening at ICERs > 50’000 $/LY

<table>
<tr><th>Primary screening test, post-switch</th><th>Total cost per woman ($)a</th><th>ICER ($/YLS)</th></tr>
<tr><td>no screening</td><td>120</td><td>—</td></tr>
<tr><td>HPV 6y, 12m time to rescreen</td><td>760</td><td>29000</td></tr>
<tr><td>cytology 3y</td><td>1001</td><td>Dominated</td></tr>
<tr><td>HPV 5y, 12m time to rescreen</td><td>822</td><td>57000</td></tr>
<tr><td>HPV 4y, 12m time to rescreen</td><td>922</td><td>76000</td></tr>
<tr><td>HPV 4y, 6m time to rescreen</td><td>971</td><td>98000</td></tr>
<tr><td>HPV 3y, 6m time to rescreen</td><td>1160</td><td>144000</td></tr>
<tr><td>HPV 3y, 6m time to rescreen, colposcopy after 1 repeated HPV+/cyt-</td><td>1200</td><td>513000</td></tr>
</table>

ICERs are generally higher than in many other studies, however in this Norwegian study some indirect medical and some societal costs such as women’s travel and time for screening, diagnostic follow up and treatment were taken into account.</td>
</tr>
</table>

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b What is the best age to start using HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
Goldhaber-Fiebert et al. 2008 USA [35]	Goal: to evaluate for women who are not vaccinated, what recommendations can be made regarding cervical cancer screening guidelines, taking into account new data on the performance of HPV DNA testing A cohort of unvaccinated women of 9 years until x was modelled Strategies • Cytology with HPV triage • HPV with cytology triage • cotesting Frequency: 1/2/3 and 5-yearly, start age for screening was varied between 18/21 and 25 years Perspective: societal perspective including medical costs, staff time, patient time and transport cost for screening, diagnostic follow up and cancer treatment, however no indirect costs	QALYs and lifetime risk of cancer were taken as effectiveness measures. Only strategies with ICER < 200'000$/QALY and are on the cost effectiveness frontier are shown. 3-yearly cytology based testing was dominated, but is shown for clinical effects as reference. Strategies are coded as follows Start age with cytology, switch age, strategy after switch ("cyt" for cytology with HPV triage or "HPV" for HPV with cytology triage), frequency in years, Strategy / % reduction cancer risk compared to no screening / QALYs no screening - 26.67212 25, none, cyt, 5y 50.9% 26.71857 Any, none, cyt, 3y 61.5% 26.72766 25, 35, HPV, 5y 61.6% 26.72609 25, 30, HPV, 5y 62.3% 26.72733 25, 35, HPV, 3y 70.7% 26.73237 25, 30, HPV, 3y 71.5% 26.73344 21, 30, HPV, 3y 72.2% 26.73493 21, 30, HPV, 2y 76.3% 26.73769 The burden of screening was not directly addressed apart from time and travel cost of women for screening, diagnostic follow up and treatment. No numbers of colposcopies or women being in triage were compared between studies. QALYs had no disutilities assigned to screening, being in triage or being treated for CIN2/3.	Screening was always started with cytology and switched to HPV based testing at ages 25, 30 or 35, with the exception of one scenario with HPV testing starting at age 18 The authors recommend starting HPV based testing at 30 years from an overall cost effectiveness analysis (no burden of individual strategies were compared)	3-yearly cytology based testing was dominated; its cost is shown as reference. Strategy / cost $ / ICER $/QALY no screening 153 25, none, cyt, 5y 471 7'000 Any, none, cyt, 3y 655-848 dominated 25, 35, HPV, 5y 562 12'000 25, 30, HPV, 5y 598 29'000 25, 35, HPV, 3y 787 37'000 25, 30, HPV, 3y 844 53'000 21, 30, HPV, 3y 960 78'000 21, 30, HPV, 2y 1297 122'000 Based on these data 3-yearly HPV with cytology triage testing is cost effective at an ICER of 53'000 $/QALY starting with cytology based testing at age 25 and switching to HPV based testing at age 30 Cotesting was only on the cost efficiency frontier with a strategy costing > 3Mio$/QALY, all other cotesting strategies were dominated

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b What is the best age to start using HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
	Results reported in 2004 US$ Costs and benefits discounted at 3% Quality score: 0.80 Transferability data score: 0.90			

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start HPV	Research Question 1c comparison of (Incremental) cost effectiveness ratios
MSAC 2014 Australia [29]	Goal: to evaluate strategies for policy renewal in the Australian cervical cancer screening program. A cohort of unvaccinated women was modelled (in addition a vaccinated cohort was modelled) Strategies 1. Current practice 2- yearly cytology at 18-69 years, with HSIL referred to colposcopy. For LSIL either colposcopy or retesting after 6 months 2. conventional cytology-based screening 3-yearly for age 25-49 and 5-yearly for age 50-64 (IARC intervals) 3. LBC instead of Pap test (IARC intervals) 4. Cytology with HPV triage 5. HPV with cytology triage 5-yearly 6. HPV with partial genotyping. HPV 16/18 goes directly to colposcopy, other	No comparator was analyzed that equals the Swiss recommended screening of 3-yearly cytology with HPV triage after 3 annual tests in younger women. Current practice in Australia is 2-yearly Pap test with Pap retest. The closest comparator to Swiss screening is cytology with HPV triage with 3 yearly testing from 25 to 49 and 5-yearly testing from 50-65 and an exit test at age 69. Results of the best selected strategies show that HPV with cytology triage is more effective in reducing cancer incidence that cytology only or cytology with HPV triage at higher frequency at 25-49 years. Cotesting has the same effect as HPV with cytology triage. HPV16/18 genotyping yielded the best result Strategies — cancer incidence ASR/100'000 — discounted life years 1. Current practice 2y — 6.9 — not shown 2. Cytology only IARC — 7.6 — 21.62678 3. Pap +HPV triage IARC — 6.2 — 21.62760 4. LBC + HPV triage IARC — 6.1 — 21.62764 5. HPV + cyt triage 5y — 5.8 — 21.62779 6. HPV16/18 genotyping 5y — 5.7 — 21.62792 7. Cotesting 5y — 5.8 — 21.62783 Burden of screening: Strategies — number of colposcopies 1. Current practice 2y — reference 2. Cytology only IARC — -12% 3. Pap +HPV triage IARC — +13% 4. LBC + HPV triage IARC — +16% 5. HPV + cyt triage 5y — +20% 6. HPV16/18 genotyping 5y — +37% 7. Cotesting 5y — +33%	Not addressed HPV testing was applied starting at age 25	HPV based strategies are at the efficiency frontier and dominated cytology based strategies Cotesting has similar effectiveness as HPV only as the primary test at a higher cost (dominated) HPV with genotyping is more effective regarding LYG at a higher cost than HPV without genotyping Strategies — total cost Australian Mio — cost per woman $ — ICER $/LY 1. Current practice 2y — 214.7 — not shown — dominated 2. Cytology only IARC — 162.3 — 277 — reference 3. Pap +HPV triage IARC — 193.1 — 337 — dominated 4. LBC + HPV triage IARC — 203.5 — 358 — dominated 5. HPV + cyt triage 5y — 175.5 — 310 — 33'000 6. HPV16/18 genotyping 5y — 181 — 323 — 100'000 7. Cotesting 5y — 217.1 — 378 — dominated If QALYs are compared, with QALY set 1 HPV with genotyping has similar effectiveness that HPV without genotyping, with QALY set 2 HPV without genotyping is more effective. QALY Weight Set 1 utilized a new set of weights from a study recently conducted in metropolitan Sydney, which was specifically designed to obtain weights relevant to cervical screening and HPV vaccination in an age-representative sample of women invited for screening. This set of weights assigned some disutility to the experience of being screened, even if the test result was negative. The MSCA recommends switching to 5-yearly HPV testing with HPV16/18 genotyping in women of 25-69 years.

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start HPV	Research Question 1c comparison of (Incremental) cost effectiveness ratios
	hrHPV to cytology triage 5-yearly 7. Cotesting, 5yearly equency: as above Perspective: health system Results reported in 2013 Australian $ Costs and benefits discounted at 5 % Quality score: 0.89 Transferability data score 0.83			

<table>
<tr><th>Publication Year Country</th><th>Study Description</th><th>Research Question 1
What test results in the highest clinical effectiveness at the lowest burden of follow up?</th><th>Question 1b best age to start HPV</th><th>Research Question 1c
comparison of (Incremental) cost effectiveness ratios</th></tr>
<tr>
<td>Vijayara-ghavan et al.
2010
Canada
[33]</td>
<td>Goal: to determine the potential cost-effectiveness of including HPV tests for cervical cancer screening for Quebec, Canada.

A cohort of unvaccinated women of 13 years until end of life was modelled. Screening in younger women was done with Pap tests, at age 30 strategies switched as follows:

• No screening;
• Cytology only (1/2/3 yearly)
• Cytology with HPV triage ASC-US (1/2/3 yearly)
• HPV with cytology triage (3 yearly)
• Co- testing (3 yearly)
• HPV only (direct referral to colposcopy if HPV-positive (3yearly)
Perspective: Health System
Results reported in 2007 Canadian $
Costs and benefits discounted at 5%
The quality score was only 0.73 and transferability data score 0.77, as some data are only available in supplements and until June 09, those supplements could not be obtained from the author yet.</td>
<td>Cancer cases and QALYs were taken as effectiveness measures. Disutilities were assigned to CIN and Cancer stages. Burden was briefly discussed as number of expected colposcopies.

Screening strategies with 3-yearly HPV as primary screening test were more effective in reducing cervical cancer incidence than annual cytology based testing

<table>
<tr><th>Screening Strategy*</th><th>Annual Cervical Cancer Incidence</th><th>QALY</th></tr>
<tr><td>No screening</td><td>1’282</td><td>17.7817</td></tr>
<tr><td>Cytology only 3y</td><td>339</td><td>17.8196</td></tr>
<tr><td>Cytology+HPV triage 3y</td><td>291</td><td>17.8215</td></tr>
<tr><td>Cytology only 1y</td><td>191</td><td>17.8259</td></tr>
<tr><td>HPV+cytology triage 3y</td><td>163</td><td>17.8263</td></tr>
<tr><td>Co- testing 3 y</td><td>163</td><td>17.8263</td></tr>
<tr><td>Cytology+HPV triage 1y</td><td>147</td><td>17.8270</td></tr>
<tr><td>HPV only 3y</td><td>145</td><td>17.8272</td></tr>
</table>

The HPV only strategy had the highest colposcopy rates of 2’000 per 100’000 women, while HPV with cytology triage or cotesting had 55-59% fewer colposcopy rates (830) compared to cytology based strategies with 160-700 colposcopies</td>
<td>Not addressed
Screening strategies started at 30 years</td>
<td>“All strategies incorporating HPV testing as a primary screening test were more effective and less expensive than annual cytology alone, while HPV testing to triage equivocal Pap smears annually was very cost-effective ($2,991 per QALY gained compared to annual cytology alone). When compared to cytology every three years, HPV-based strategies cost an additional $8,200 to $13,400 per QALY gained.”

<table>
<tr><th>Screening Strategy*</th><th>Average Lifetime Costs ($)</th><th>ICER $/QALY</th></tr>
<tr><td>No screening</td><td>368</td><td></td></tr>
<tr><td>Cytology only 3y</td><td>753</td><td>dominated</td></tr>
<tr><td>Cytology+HPV triage 3y</td><td>750</td><td>9’’600</td></tr>
<tr><td>Cytology only 1y</td><td>926</td><td>dominated</td></tr>
<tr><td>HPV+cytology triage 3y</td><td>809</td><td>12’300* (dominated)</td></tr>
<tr><td>Co- testing 3 y</td><td>843</td><td>Dominated</td></tr>
<tr><td>Cytology+HPV triage 1y</td><td>930</td><td>Dominated</td></tr>
<tr><td>HPV only 3y</td><td>815</td><td>11’400*</td></tr>
</table>

* ICERs for HPV with cytology triage and the HPV only strategy were calculated against 3 yearly cytology with HPV triage.
HPV only dominated HPV with cytology triage. However this strategy may not be acceptable due to the more than two times higher colposcopy rates.</td>
</tr>
</table>

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start with HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
Vijayara-ghavan et al. 2010 USA [36]	Goal: to evaluate the cost-effectiveness of HPV 16/18 genotype triage in the US health care setting. A cohort of unvaccinated women of 30 years until end of life was modelled Strategies • LBC 2 – yearly • LBC with HPV triage, 2-yearly • HPV with LBC triage, 3-yearly • cotesting, 3-yearly • cotesting with HPV 16/18 genotyping 3-yearly • HPV with 16/18 genotyping In the strategies with HPV genotyping women being HPV 16/18 positive were referred to colposcopy, those positive for other hrHPV types were referred to cytology triage Frequency: as described above Perspective: health care payer Results reported in 2007 US $ Costs and benefits discount rates no discounting described Quality score: 0.86 Transferability data score: 0.90	2-yearly LBC with or without HPV triage was less clinically effective than all HPV based screening methods with 3-yearly intervals The most clinically effective strategy in terms of cancer incidence was co-testing with HPV 16/18 genotyping, followed by co-testing, followed by HPV with HPV16/18 genotyping. In terms of QALYs the most effective strategy was cotesting with HPV 16/18 genotyping, followed by HPV with HPV16/18 genotyping, followed by co-testing. This is due to lower mortality. Strategies — cancer incidence — QALYs LBC — 9.17 — 28.6623 LBC with HPV triage — 8.56 — 28.6651 HPV with LBC triage — 7.86 — 28.6670 cotesting — 7.49 — 28.6714 cotesting. + genotyping — 6.62 — 28.6745 HPV with genotyping — 7.57 — 28.6725 The burden of screening was not addressed, QALYs assigned disutilities to CIN and cancer not to being screened per se or to being in triage after positive test result	Not addressed The model chose 2-yearly cytology for all women until a switchover age of 30	No comparator was used that was equivalent to the Swiss recommended screening of 3-yearly cytology with HPV triage 2-yearly LBC with HPV triage was dominated by 3-yearly HPV testing with LBC triage ICERs are shown compared to next less effective strategy Strategies — ICER /$/QALY) LBC — - LBC with HPV triage — dominated HPV with LBC triage — 13’617 cotesting — 17’204 cotesting. + genotyping — 33’807 HPV with genotyping — 34’074 All HPV based strategies were cost effective with ICERs ranging from 13’617 $ /QALY for HPV with LBC triage to HPV with 16/18 genotyping and cotesting with 16/18 genotyping with ICERs around 34’000$/QALY

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start with HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
Diaz et al. 2010 Spain [77]	Goal: the primary goal of the study is to assess the health and economic impact of adding HPV vaccination to cervical cancer screening. In addition the study compares different screening strategies for vaccinated and unvaccinated women. A cohort of women of 9 years until end of life was modelled Strategies 1. Cytology alone 2. Cytology with HPV triage 3. Cotesting Frequency: 1/2/3/4/5-yearly starting at 25 years Perspective: direct medical cost plus cost of patient time and transport for screening and diagnostic follow up. Results reported in 2005 € Costs and benefits discounted at 3% Quality score: 0.76 Transferability data score: 0.70	Reporting on effectiveness of alternatives was not in a level of detail that allowed comparison of effects, harms and costs of the current Swiss screening algorithm (3-yearly cytology only or cytology with HPV triage). This strategy was dominated and no details were reported on it. In general the graphs show that cotesting every 5 years is as effective as cytology only or cytology with HPV triage every 3 years.	Not addressed HPV testing was added to cytology in the cotesting cohort at 35 or 40 years	Reporting on effectiveness of alternatives was not in a level of detail that allowed comparison of effects, harms and costs of the current Swiss screening algorithm (3-yearly cytology only or cytology with HPV triage). This strategy was dominated and no details were reported on it.

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start with HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
Kulasingam et al. 2009 Canada [34]	Goal: To determine the potential cost-effectiveness of including HPV tests for cervical cancer screening for Canada and three provinces: Alberta, Newfoundland and Ontario A cohort of unvaccinated women was modelled Strategies • Pap test, yearly at age 18-21 thereafter 3-yearly (current practice) • Pap test only 1 or 2 yearly • LBC • HPV only (direct referral to colposcopy), 3 or 5-yearly • Cotesting, 2/3/5-yearly (in this case either HPV or Pap positive is directly referred to colposcopy) • Pap with HPV triage (1-yearly) • HPV with Pap triage (3 or 5 yearly) (it is not clearly described, after how much time HPV+/Pap- women are rescreened) Perspective: health system Results reported in 2006 Canadian $ Costs and benefits discounted at 3% Quality score: 0.78 Transferability data score:0.80	The study did not have a comparator of cytology with HPV triage with 3-yearly frequency. The closest comparator to the Swiss strategy is 3-yearly Pap testing. Concerning the burden of screening the number of false positive test results (Pap or HPV) was reported. HPV based methods with Pap triage starting at age 25 yielded fewer cancer cases than current practice with Pap testing (which starts screening at the age of 18) Cancer cases / false positives Pap test only 809 / 20'529 HPV + Pap triage 5y 736 / 2'871 HPV + Pap triage 3y 467 / 5'585 Cotesting 2y 229 / 82'340 HPV only (with direct referral to colposcopy) and cotesting of cytology and HPV (with direct referral to colposcopy if either test was positive) led to disproportionately high numbers of false positive tests	The study modelled HPV with Pap triage starting at either 18 or 25 years With 3 yearly screening cancer cases were reduced by 6% when starting at 18 years with HPV testing but increased false positive results by a factor of 1.8 vs starting at 25 years and increased the ICER twofold to 47'319 $ With 5 yearly screening only 25 years was on the cost effectiveness frontier as the switch age	Numbers for false positives and cancer cases and ICERs for dominant strategies were reported in numbers; however LY and cost are only presented graphically. The current screening strategy with Pap test, yearly at age 18-21 thereafter 3-yearly, was dominated in being less effective and more costly than HPV based testing with Pap triage starting at age 25. The ICER of 5-yearly HPV with Pap triage against no intervention was 6'720 Canadian $. 3-yearly HPV with Pap triage starting at 25 years was the next most cost effective strategy and had an ICER of 24'257 Canadian $. 2 yearly cotesting was on the cost effectiveness frontier, however at a very high ICER of 432'751 Canadian $ HPV only with direct referral to colposcopy was not on the cost effectiveness frontier

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start with HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
Chuck 2010 Alberta, Canada [78]	Goal: To evaluate screening strategies for Alberta, Canada A cohort of unvaccinated women of 12 years until 80 was modelled Strategies • Pap test • LBC • Pap with HPV triage • HPV with LBC triage all ages • HPV with LBC triage ≥ 30 years Frequency: 1/2/3/4/5 yearly Perspective: health system Results reported in 2007 Canadian $ Costs discounted at 5% and benefits at 3% Quality score: not calculated Transferability data score: not calculated	QALYs were taken as effectiveness measures. Disutilities were assigned to CIN and Cancer stages, not to screening itself. However effectiveness data were only presented graphically and highly aggregated, so no detailed analysis of the results was possible. This was considered a knock-out criterion for the study and a quality score and transferability data score was not calculated. Still it is curious from the graphical representation that in this study HPV based strategies seem to be less effective than cytology based strategies, which is different than findings from another study for Alberta, Canada ([34] and practically all other models. 3-yearly Pap testing with HPV triage is recommended No detailed analysis was possible for the cause of this finding due to the missing details in the results presentation	Cannot be derived from this study	Cannot be derived from this study

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start with HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
Mühlberger 2008 Germany [74]	Goal: Systematic Review of Health Economic Evidence for HPV based screening vs Pap test Commissioned by the DAHTA@DIMDI, a subsidiary of the German Federal Ministry of Health 12 decision-analytic cost-effectiveness models up to March 2006 were analyzed. Quality score and Transferability data score of the EURONHEED checklist was not applied as this is a systematic review of health economic studies not a health economic study itself	Not addressed, focus was on cost effectiveness	Not addressed	The authors conclude that "the introduction of HPV-based screening programs is cost-effective if the screening interval of the established Pap program exceeds 2 years. In settings with biennial Pap screening, introduction of HPV-based screening is unlikely to be cost-effective, as clinical effectiveness of both test methods is comparable with HPV testing being more costly. Results also suggest cost-effectiveness of HPV-based screening in settings with annual Pap screening, where clinical effectiveness of HPV based screening at frequencies ≥ 2 years is comparable while costing less. This finding is based on the assumption of 100% screening attendance in the annual Pap screening, which is much higher than annual attendance rates in Germany (about 50%).

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start with HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
Berkhof et al. 2010 Netherlands [79]	Goal: A cohort of unvaccinated women modelled Strategies • Cytology only • Cytology with HPV triage • HPV with cytology triage • cotesting Frequency: 5-10 years Perspective: societal (including travel time and productivity loss) Results reported in 2007 € Costs discounted at 4% and benefits at 1.5%	The motivation of this study is the analysis of cost-effectiveness of primary HPV screening for cervical cancer in the Netherlands. For transferability of this study on the Swiss context, a calculation of screening frequency higher than 5-yearly as currently applied in the Swiss setting is missing. Therefore this study cannot be directly used for the transferability analysis and was not further analyzed. In short: “In comparison to 5-yearly cytology, 5-yearly HPV testing with cytology triage gave a reduction in the number of cancer cases of 23% (range, 9–27%). The reduction was 26% (range, 10–29%) for combination testing and 3% (range, 21 to 8%) for cytology with HPV triage. For strategies with primary HPV testing, the model also estimated a reduction in cancer cases when the screening interval was extended to 7.5 years. 5-yearly cytology with HPV triage and 5 to 7.5-yearly HPV testing with cytology triage were cost effective (ICER below Dutch willingness-to-pay threshold of €20,000/QALY).”		

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start with HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
van Rosmalen et al. 2012 Netherlands [31]	Goal: the analysis of cost-effectiveness of primary HPV screening for cervical cancer in the Netherlands. A cohort of 8 Mio unvaccinated women born from 1939 to 1992 was modelled with the new simulated screening strategies starting at 2011 (as described by [80]) Strategies • Cytology only • Cytology with HPV triage • HPV with cytology triage Frequency: comparator 5 yearly Perspective: society (In addition to medical costs, costs for an invitational system, registration, quality assurance, and time and travel cost of women was calculated) Results reported in 2010 € Costs and benefits discounted at 3% Quality score: 0.86 Transferability data score: 0.90	For transferability of this study on the Swiss context, a calculation of screening frequency of 3-yearly as currently applied in the Swiss setting is missing. Therefore this study cannot be directly used for the transferability analysis and will not be described in detail In short: cytology only based testing was dominated and the authors come to the conclusion that primary HPV testing with cytology triage is the most cost-effective strategy With a cost effectiveness threshold of 20'000 or 50'000 €/QALY gained only 3 screening rounds (10-yearly, less effective than current practice) or 7 screening rounds (6-yearly, more effective than current practice) would be applied	For women aged 32 and younger primary cytology screening is more cost-effective than primary HPV testing	

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start with HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
de Kok et al. 2012 Netherlands [80]	Goal: "To investigate, using a Dutch model, whether and under what variables framed for other European countries screening for human papillomavirus (HPV) is preferred over cytology screening for cervical cancer, and to calculate the preferred number of examinations over a woman's lifetime." A cohort of 8 Mio unvaccinated women born from 1939 to 1992 was modelled with the new simulated screening strategies starting at 2011. For the six scenarios that reflect differing background risks and test performances for cervical cancer screening in Europe, the predicted costs and QALYs gained were determined. Strategies 1. Cytology only 2. Cytology with HPV triage 3. HPV with cytology triage Frequency: 3-10 yearly Perspective: societal including women's travel and time Results reported in 2009 € Costs and benefits discounted at 3% Quality score: 0.88 Transferability data score: 0.91	Primary HPV screening was superior to cytology screening in most of the scenarios that were simulated in the model Scenarios were varied by • background cancer risk without screening (mortality of 5, 7.5 or 10 / 100'000 life years) • Prevalence of HPV "low" or "High" (based on background cancer risk) • Sensitivity of cytology (60 or 75%) • Cost of HPV testing (21 or 33 €) • Sensitivity of HPV (90 or 95%) According to the definitions of deKok Switzerland might potentially fall into the following categories based on data or conservative estimates • Average background cancer risk without screening (based on ASR of cervical cancer mortality of 8 in 1970-74 when cervical cancer screening had just begun, source: Federal Office of Statistics (www.bfs.admin.ch/bfs/portal/de/index/.../14/.../02.Document.110237.xls, last accessed 8 March 2016) • Prevalence of HPV "High" (conservative estimate based on prevalence graphs in [62]) • Sensitivity of cytology "high" (conservative assumption of high performance of the status quo) • Cost of HPV testing "high" (based on the cost structure in Switzerland and no fixed price yet for HPV as a screening test) • Sensitivity of HPV "high" (based on internationally clinically confirmed data of HPV test performance) Under these assumptions cytology based screening is the most cost effective strategy with 5, 6 or 8 screening events between the ages 30-55 or 65 with ICERs under 20'000 , 30'000 and 50'000 €/QALY. As all of these strategies have 5 yearly cytology screening and thus fewer screening events than current screening in Switzerland, these strategies will be less effective than current screening in Switzerland. No numbers for clinical benefits or burden of screening were shown. Thus no quantitative results for 3-yearly cytology are available from this study.		

Publication Year Country	Study Description	Research Question 1 What test results in the highest clinical effectiveness at the lowest burden of follow up?	Question 1b best age to start with HPV?	Research Question 1c comparison of (Incremental) cost effectiveness ratios
Dillner 2013 Country independent [81]	Review of existing health economic studies , however not systematic (Methods of systematic review not described) This study is discussing results from a HTA published in Italian [108] and of the study of de Kok. [80], which is separately analyzed in this thesis. Therefore no repetition of the results in this table is done. The study reports rather general thoughts and conclusions than quantitative results, however content for research question 2 on the feasibility of HPV based screening			

17 Appendix 5: "Research question 2 – Excerpt of answers"

17.1 Excerpt of Answers to Research Question 2 from systematic reviews and meta-analyses

Table 11: Excerpt of information on research question 2 from the clinical systematic reviews and meta-analyses

Systematic Review / Meta-analysis	Research Question 2 In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implementing screening based on HPV testing identified? If yes, which barriers are these? Are they relevant for the Swiss health care setting?	Concern category
Huh, 2015, USA [64]	"To achieve the maximum benefit of screening we need to continue to identify women who are either unscreened or under-screened." "As with all new advances that enter clinical practice, the introduction of primary hrHPV screening raises a number of questions and concerns. Despite the improved sensitivity associated with primary hrHPV testing compared to cytology, clinicians should be aware that false negative results will continue to occur. Specimen adequacy, appropriate internal controls, and the impact of potential interfering substances (e.g., lubricants) are also important considerations when applying primary hrHPV testing to a screening population. Assay internal controls may not always reflect adequate sampling and do not completely obviate the risk of false negatives without the added morphologic control offered by cotesting. Data in this area are limited and further research is necessary." "The 2011 ACS/ASCCP/ASCP Cervical Cancer Screening Guidelines stressed the importance of using FDA-approved tests that also met specific criteria for clinical performance. At present, there are four FDA approved hrHPV assays that are commercially available, but only one of these assays is now FDA-approved specifically for primary screening. Since the performance characteristics vary somewhat among these four FDA-approved assays, assumptions of comparability should not be made. As such, clinicians should not use an FDA-approved test without a specific primary hrHPV screening indication. Clinicians who wish to offer primary hrHPV screening to their patients are advised to inquire with their respective testing laboratories as to which hrHPV test is currently used and whether it is FDA-approved for primary screening." "Concerns regarding harmonizing primary hrHPV screening algorithms with published screening, management, and treatment guidelines and the inherent confusion this alternate strategy might create for both patients and providers exist. Further investigation is also needed on understanding how women might transition in and out of different algorithms of cytology, cotesting, and primary hrHPV screening. Finally, there remain a number of questions with regard to adoption, implementation, and acceptance."	1 underscreened 2 false negatives 3 clinically validated HPV tests 4 alternate policies 5 change of policy
IQWiG 2011, 2014 Germany [46, 65]	„Deshalb sind im Fall einer Änderung der Screeningstrategie des Zervixkarzinomscreenings im Rahmen der jährlichen gynäkologischen Vorsorgeuntersuchung in Deutschland mögliche Konsequenzen hinsichtlich anderer gynäkologischer Erkrankungen zu berücksichtigen." „Die aktuellen europäischen Leitlinien halten sich mit Empfehlungen zu einem primären Screening auf hrHPV-Infektionen zurück.	6 side effects of longer screening intervals

Systematic Review / Meta-analysis	Research Question 2 In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implementing screening based on HPV testing identified? If yes, which barriers are these? Are they relevant for the Swiss health care setting?	Concern category
	Ein primäres hrHPV-Screening ohne die Definition der Altersgruppe, des Screeningintervalls und der wesentlichen Elemente einer Qualitäts-sicherung bei der Programmimplementierung wird nicht empfohlen [47,50]. Im Rahmen eines opportunistischen Screenings wird ein hrHPV-Screening ebenfalls nicht empfohlen, weil unter solchen Bedingungen das Einhalten der empfohlenen Screeningintervalle und die erforderliche Qualitätskontrolle nicht gewährleistet werden können. Stattdessen werden Pilotstudien mit einem validierten HPV-Test empfohlen, wenn sie im Rahmen eines organisierten Screeningprogramms mit sorgfältigem Monitoring und systematischer Evaluation der gewünschten Zielgrößen, Nebenwirkungen und Kosten stattfinden. Eine Ausweitung auf das gesamte Land solle erst dann erfolgen, wenn sich das Pilotprojekt als erfolgreich in Bezug auf die Effektivität und Kosteneffektivität erwiesen habe und wenn zentrale organisatorische Probleme adäquat gelöst worden seien.“	7 organized screening program 8 Quality Control 9 Adherence to screening protocols 10 Monitoring of effects 11 Pilotproject
Pileggi, 2014, [47]	Not addressed	-
Arbyn 2012, [44]	“The possible advantages offered by HPV-based screening require a well-organized program with good compliance with screening and triage policies.”	7 organized screening program 9 Adherence to screening protocols
Patanwala, 2013, [66]	Not addressed	-
Saslow 2012, USA, [67]	“Approximately half of the cervical cancers diagnosed in the United States are in women never screened, and an additional 10 percent of cancers occur among women not screened within the past five years. Technologic improvements in screening are unlikely to have a substantial impact on mortality if they do not reach this population.” However: “HPV testing provides longer-term safety following a negative test than cytology, a useful characteristic for the infrequently screened.” “The most important research priority involves identifying strategies to increase screening coverage in unscreened or under-screened women, in whom a significant proportion of invasive cancers occur. Novel strategies utilizing HPV testing and other molecular approaches should be examined. Specifically, self-collection of cervico-vaginal specimens coupled with HPV testing can achieve sensitivity that is comparable to or better than that of cytology-based screening.” “While cotesting is preferred to cytology alone based on risks and harms assessment, such a strategy might not be feasible in all clinical settings in the U.S. due to a lack of payment for cotesting or due to local policies “ “Implications, such as cost effectiveness of and adherence to implementing such a major change in the current US opportunistic screening setting, require further evaluation and planning.” “ potential stigmatization from the diagnosis of a sexually transmitted Infection…”	1 underscreened 12 self-testing 13 reimbursement policy 9 Adherence to screening protocols 14 STI connotation

Systematic Review / Meta-analysis	Research Question 2 In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implementing screening based on HPV testing identified? If yes, which barriers are these? Are they relevant for the Swiss health care setting?	Concern category
[54], Massad 2013, USA	It is important that only validated tests for HPV with sound evidence from clinical studies are used in screening as other HPV tests may differ in their sensitivity and specificity and do not achieve the same results as in the studies on which the screening strategies are based.	3 clinically validated HPV tests
[56], ACOG, 2012, USA	KPIs should be measured to monitor adherence to recommendations, e.g.: Percentage of women tested at shorter intervals than recommended "In addition, the anxiety and stigmatization associated with HPV infection are significant concerns for women participating in cervical cancer screening programs."	10 monitoring 14 STI connotation
[43], Bouchard-Fortier, 2014	Not addressed	-
[51], Moyer, 2012, USA	"Efforts to further reduce cervical cancer morbidity and mortality need to focus also on women who have not been adequately screened." "Maintaining the comparability of the benefits and harms of cotesting and cytology alone demands that patients, clinicians and health care organizations adhere to currently recommended screening intervals, protocols for repeat testing, thresholds for colposcopy and extended surveillance"	1 Underscreened 9 Adherence
[48], Rebolj, 2012	Not addressed	-
[45], Murphy, 2012	"Whatever the triage method, it must be implemented within an organized screening program with an information system to facilitate invitations, recalls, and communication and follow-up of abnormal results. Such systems are essential, as intensified follow-up of positive results and longer screening intervals for HPV-negative women will likely be features of programs that implement HPV testing for primary screening."	7 organized program 15 call – recall 16 communication 17 triage follow up
[68], Whitlock, 2011, USA	"Besides safety, feasibility or acceptability may affect adoption of a risk-stratified policy on cervical cancer screening because primary care physicians may not currently be extending the screening interval to 3 years after negative cotesting results" "To evaluate the potential psychological effects of HPV testing, we found 4 fair-quality observational studies (54–57) that used mailed questionnaires to examine the immediate and short-term effects of HPV testing in 4104 women in the United Kingdom or Australia. Levels of immediate anxiety and distress were increased in women who tested positive for HPV compared with those who tested negative. These differences, however, were resolved by 6-month follow-up. Data on other psychosocial outcomes and longer-term follow-up were sparse."	9 adherence to protocols 21 Quality of Life
[49], Cuzick, 2008	"HPV infections are very common, especially in young women, and usually clear spontaneously, so that over-reaction to the detection of HPV DNA carries a risk of unnecessary colposcopies, psychological distress and the possibility of overtreatment. Thus, it is essential that HPV testing-based screening is introduced within an organized program with ongoing process and outcome evaluation rather than in an opportunistic setting." "The fact that HPV is a sexually transmitted infection may lead to anxiety and concerns about sexual relationships. These psychosocial aspects and the need for more information and educational programs…" "Women want their health providers to be well-informed about the disease in order to answer their questions without giving	7 organized screening 10 monitoring 14 STI connotation 18 education of

Systematic Review / Meta-analysis	Research Question 2 In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implementing screening based on HPV testing identified? If yes, which barriers are these? Are they relevant for the Swiss health care setting?	Concern category
	confusing and inconsistent information. Health professionals' knowledge of HPV has not received much attention, but the experience of women with positive test results suggests that many have limited knowledge about HPV. Education of health professionals should be a priority. Women's reactions to hearing about the test include confusion and anxiety about the association with STIs as well as issues of fidelity and trust in relationships. Anhang et al. identified confusion about the relationship between Pap testing and HPVDNA testing, and uncertainty about the level of risk. " "Women from some ethnic and religious backgrounds express fears that community leaders could be less supportive of cervical screening if they were aware of the link with sexual transmission."	health care professionals 14 STI connotation
[52], Schiffman, 2011, USA	"Of note, in the United States, cervical cancer screening is often viewed as a clinician–"patient" decision, not as a public program as it is in some other countries. Clinicians and patients may view a particular level of risk and cost differently from public health planners who are faced with limited resources." "In any case, the introduction of new HPV tests with varying test performances, new biomarkers, and the HPV vaccine will eventually make clinical algorithms regarding cervical screening and management of screening abnormalities untenably complex (…) and quickly out of date. Each round of revised algorithms will need to account for past virological, cytological, and histological test histories (…), as well as the results of any novel tests that emerge. Compared with branching algorithms, a properly constructed and validated risk assessment tool would be more powerful and easier to update and use for clinical decision making, even for clinician–patient discussions (…). The estimated risk of CIN3+ (e.g., if colposcopy were performed that day, or in 1 year, or at a 3-year follow-up) is the relatively objective, quantifiable outcome that scientists can provide as the basis for cost-effective clinical and public health decisions." "However, such a change is not likely to happen soon in the United States, where cancer prevention policies are only partly dictated by evidence regarding optimal practice. It is notable that current evidence-based guidelines for cervical cancer screening and management are being widely ignored in the United States (…). Each interest group with input into policy, including various government agencies, has its own mandates and constraints. Much of screening practice is dictated by clinical groups; in considering clinical recommendations, we should not ignore that the economic threat to practicing gynecologists and cytopa-thologists inherent in reducing the amount of screening is real."	9 adherence to protocols 18 education 19 complexity 9 adherence 20 economic threats

17.2 Excerpt of Answers to Research Question 2 from Health Economic studies

Table 12: Excerpt of answers to research question 2 from health economic studies

Publication, Country	In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implement screening based on HPV testing identified? If yes, which barriers are these?	Concern category
[37], Huh, 2015, USA	No specific barriers were identified towards implementation, however it is interesting to note, that the recommended strategy in the US for cotesting is 5-yearly, while the authors say “American Congress of Obstetricians and Gynecologists and other clinical experts have contended that 3-yearly cotesting is the more likely scenario in the community as patients are unlikely to feel comfortable with extended screening intervals”. This implies that patients’ preferences need to be taken into account when defining the recommended screening strategy, otherwise it may not be implemented as recommended and thus miss its projected clinical and cost effectiveness.	9 adherence 24 patient preferences
[30, 60], Sroczynski, 2010, 2011, Germany	The authors warn that prior to encouraging an extension of the screening interval, the effect of longer screening intervals on screening adherence and attendance at gynecological checkups should be carefully considered. In addition the authors recommend the implementation of an organized screening program for quality-controlled introduction of HPV screening with continued systematic outcomes evaluation. “The implementation of an organized screening programme for quality-controlled introduction of HPV screening and -vaccination with continued systematic outcomes evaluation is recommended. Future research is needed to acquire evidence-based information on adherence patterns and the impact of screening results on quality-of-life. On the limitation that no QALYs are available: Since screening results in a relatively small average gain in life expectancy, changes in quality-of-life due to psychological distress associated with the communication of screening results or adverse events of pre-cancer treatment may significantly affect the estimated cost-effectiveness ratios.” „Gerade aber im Screening können relativ kleine und vorübergehende Lebensqualitätsverluste durch zum Beispiel falsch-positive Testergebnisse einen grossen Einfluss auf der Populationsebene haben. Es ist anzunehmen, dass diese Lebensqualitätsverluste in Screeningsettings mit kürzeren Screeningintervallen oder hohen Teilnahmeraten stärker sind als in Settings mit längeren Screeningintervallen oder niedrigeren Teilnahmeraten.“ “ Europäische Leitlinien: Die Autoren der Leitlinien kommen zum Schluss, dass primäres HPV-Screening nicht empfohlen werden sollte, ohne die Altersgruppe, das Screeningintervall und die wesentliche Elemente für eine Qualitätssicherung bei der Programmimplementierung zu benennen. Im Rahmen eines opportunistischen Screenings wird ein HPV-Screening nicht empfohlen, weil unter solchen Bedingungen ein Einhalten der empfohlenen Screeningintervalle und die erforderliche Qualitätskontrolle nicht gewährleistet werden könne. Pilotstudien mit validierten HPV-DNA-Tests werden empfohlen, wenn sie im Rahmen eines organisierten Screeningprogramms mit sorgfältigem Monitoring und systematischer Evaluation der gewünschten Zielgrössen, Nebenwirkungen und Kosten stattfinden. (…) Unter einem organisierten Screening wird nach der Empfehlung des Europäischen Rats zur Krebsfrüherkennung die systematische Implementation eines Screeningprogramms verstanden, das die gesamte Zielpopulation erfasst und in dem Praxisleitlinien befolgt werden. Zur systematischen Implementation gehören ein Einladungssystem (call/recall	6 side effects of longer screening intervals 7 organized setting 8 Quality control 10 Monitoring and Evaluation 21 Quality of Life 9 adherence 11 pilot project 3 validated Tests 15 call/ recall 22 central database

Publication, Country	In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implement screening based on HPV testing identified? If yes, which barriers are these?	Concern category
	system), die Qualitätssicherung auf allen Ebenen sowie effektive und angemessene evidenzbasierte diagnostische und therapeutische Massnahmen. Um ein organisiertes Screeningprogramm durchzuführen, werden zentrale Datensysteme für notwendig erachtet, die eine Liste aller Personen der Zielbevölkerung und Daten über alle Screeningtests sowie diagnostischen Abklärungstests und die endgültigen Diagnosen erhalten sollen. Ein Qualitätsmonitoring des Screenings beinhaltet eine Analyse des Prozesses und der Ergebnisse des Screenings und einen zeitnahen Bericht der Ergebnisse an die Bevölkerung und derjenigen, die das Screening anbieten und durchführen. Eine solche Analyse würde erleichtert, wenn die Screeningdatenbank mit Krebsregistern und Sterblichkeitsdatenbanken verbunden werden könnte." „Die Empfehlung zur Einschränkung des Zervixkrebsscreenings durch die neuen Altersgrenzen und eine Verlängerung des Intervalls auf 2 Jahre sind in der US-amerikanischen Öffentlichkeit zum Teil als reine Sparmassnahmen im Zusammenhang mit der Gesundheitsreform des Präsidenten Obama interpretiert worden. Zusätzlich wurde bezweifelt, dass Ärzte und Patienten den neuen Leitlinien folgen würden. Argumente von ärztlicher Seite waren, (…) dass generell bei einem Aufruf an die Öffentlichkeit, weniger zu tun, gerade Hochrisikogruppen diese Botschaft aufnähmen und dann gar nicht zum Screening gingen. Von Patientenseite wird das Gefühl grösserer Unsicherheit angeführt, wenn man jährliches Screening gewöhnt sei. Den möglichen negativen Folgen eines Screenings (Überdiagnostik und –behandlung, ggf. Lebensqualitätseinschränkungen) wurde jedoch wenig Beachtung geschenkt. Während die Maximierung des Nutzens durch frühes und wiederholtes Screening erreicht werden kann, wird eine Minimierung des Schadens eher durch eine stärkere Fokussierung des Screenings erzielt. Das Spannungsverhältnis zwischen diesen beiden Zielen führt oft zu Kontroversen im Hinblick auf das Alter für Screeningstart und –ende und der Screeningintervalle. Leitlinien, die empfehlen weniger zu tun werden häufig mit Misstrauen betrachtet. Der US-Regierung wird ein primär wirtschaftliches Interesse an einer Reduktion von Screeninguntersuchungen unterstellt, ein wirtschaftliches Interesse ärztlicher Berufsgruppen an kurzen Screeningintervallen bleibt hingegen unerwähnt." „Opportunistisches Screening ist gekennzeichnet durch zu häufige Tests, niedrige Teilnahmeraten bei älteren Frauen, sozioökonomisch benachteiligten und Hochrisikogruppen, eine heterogene Qualität und unkontrollierte Einführung neuer Technologien und einem geringen Grad an Monitoring"	23 trust in policy makers 6 side effects of longer screening intervals 24 patient preferences 20 economic threats
[75], Bistoletti, 2008, Sweden	No barriers were discussed	
[2],Kitchener, 2014, UK	"Compliance with surveillance and optimal management of HPV-positive/cytology-negative women after primary HPV screening is of key importance". A less well-understood area relates to the response of women to being told they are HPV positive/cytology negative in terms of understanding the need for follow-up and at the same time avoiding anxiety and uncertainty." "Compliance with surveillance and optimal management of HPV-positive/cytology-negative women after primary HPV screening is of key importance. High compliance with early recall is predicted to be critical and careful attention should be paid to this aspect." "Because triage testing with cytology has imperfect sensitivity, some women in this group will be at risk of progression. Delay in follow-up in this group would result in a higher proportion of women with disease progression. Furthermore, compliance with follow-up in this	9 adherence 21 Quality of Life 17 triage follow up of abnormal results

Publication, Country	In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implement screening based on HPV testing identified? If yes, which barriers are these?	Concern category
	group is extremely important. "This study and economic evaluation lend support to convert from cytology to HPV-based screening, piloting of which commenced in the English programme in the second quarter of 2013."	 11 Pilot project
[28],Arbyn, 2015, Belgium	The authors state that implementation of such a new screening algorithm should have measures to drive adherence to screening guidelines in place as well as quality control over screening tests. The background is that currently in Belgium screening guidelines are not followed. Screening tests on cervical smears are taken much more often than every three years and colposcopies are performed on about 50% of the screened women, often at the same time as the smear was taken and not as a follow up of an abnormal primary cytological test. The frequencies of overscreening has declined since reimbursement is more strictly handled, so that only screening tests are reimbursed that occur within the recommended schedule. The need for quality control is inferred from the observation that there seems to be high heterogeneity between cytological laboratories. Heterogeneity of HPV testing should be lower than that of cytology, as the HPV test involves more automation than cytology testing. Quality control should be also implemented for colposcopy "Results of HPV testing are greatly impacted by the assay and therefore, all steps of HPV detection and typing used by a global network need careful standardization." "External quality control, HPV reference laboratory that develops standards that can be used for Quality control by laboratories An additional task is the development of international standard materials which facilitate inter-laboratory comparisons and improves laboratory performance. Laboratories identifying correctly 50 international units (IU) of HPV16 and HPV18 and 500 IU of other high-risk HPV genotypes are considered proficient. Successive proficiency studies have demonstrated improved proficiency among participating laboratories The following European countries have a national HPV reference laboratory: Czech Republic, Denmark, England, France, Germany, Italy, Norway, Scotland, Slovenia, Switzerland, Sweden. " "The clinicians are informed on the test results and are responsible to inform the screened woman and to organize the aftercare (secondary examinations and treatments). However, since the letter is directly send to the eligible women, the GPs are often unaware about the frequency of screening tests of their patients. This situation hampers the central role of the GP in sensitizing the woman about prevention of (cervical) cancer. The organization of a uniform sensitization program of the eligible women is in progress, but currently different organizations and sensitizations programs still exist, which could increase the risk to disseminate different messages. An evidence-based, objective and comprehensible patient leaflet which contains the advantages and disadvantages of cervical cancer screening, could facilitate the informed decision making by the woman." "A key issue in the adherence to the recommended European, national or regional guidelines is the reimbursement policy. In Belgium,	9 adherence 8 Quality Control 3 clinically validated HPV assays 8 Quality Control 25 external reference laboratory 26 central role of the GP 16 communication 13 reimbursement

Publication, Country	In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implement screening based on HPV testing identified? If yes, which barriers are these?	Concern category
	for instance, adaptation of the EU policy (screening every three years) in Flemish guidelines was hardly followed, since the reimbursement was not conditioned by the respect of the recommended screening interval4. However, the adoption of a new rule of reimbursement (restricted to one cytological screening examination once every two years) resulted in a 41% reduction in the total annual volume of examined Pap smears. It is expected that further restriction of reimbursement (once every three years) will further reduce the amount of over-screening"	policy
	"However, loss to follow-up should be taken into account when triage involves more visits. Avoiding the necessity for repeat testing reduces the risk of loss to follow-up. In the two Dutch trials, the compliance with follow-up after six and twelve months was ~60% and ~75%, repectivey28, 112. Other studies have also demonstrated considerable loss to follow-up at repeat testing, particularly after normal cytology. Therefore more sensitive one step reflex-triage scenarios are interesting as well, such as T1: ASCUS+ combined with HPV1618 genotyping, which results always in a good PPV (≥10%) in low- and intermediate risk situation and an acceptable NPV in low- risk situation. "	17 triage follow up
	Currently the following HPV DNA tests can be considered as clinically validated according the Meijer guideline: Abbott RT hrHPV test, COBAS-4800, Papillocheck, and two PCR assays targeting (E6/E7) of separate high-risk HPV types. However, the list is changing rapidly and an updated list should be consulted.	3 clinically validated tests
[76],Accetta, 2010, Italy	No barriers were identified towards implementation Instead the authors argue that the money saved from switching to HPV based screening and a 5 year interval from 3 year can be used for measures to improve attendance at and compliance with screening.	No barrier, but favorable for the 1 underscreened
[32],Burger, 2012, Norway	The authors warn that loss to follow up may occur and "Norwegian women are more likely to ignore recommendations to follow-up equivocal and low-grade results compared to those indicating a high-grade lesion (Nygard et al 2006). If the importance of continuing to follow up an HPV+/Cyt – negative result is not communicated adequately to women, the additional sensitivity of HPV testing could be eroded". Indeed a later study by Burger [109] on failures of screening systems cited the 2008 annual report population-based screening against cervical cancer (Oslo: Cancer Registry of Norway, 2009) saying that only 65% of eligible women attend cytology-based screening every 3 years, but the rest either never attend or less frequently than recommended. In addition at least 35% of women with abnormal results fail to return within 1 year for follow-up testing.	17 triage follow up
	"The optimal strategies identified by this analysis will require a comprehensive and dynamic system, which can alert women according to their individual screening needs. More complex and tailored screening algorithms will be more difficult to understand, not only for women, but also for clinicians, who are responsible for explaining and implementing strategies. Extensive monitoring of the coverage, compliance, resource use, and outcome variables is also crucial in order to allow the public health officials to identify caveats and areas that are in need of improvement. "	19 complexity 10 Monitoring
	Burger [109] showed that increasing compliance with screening reduces cancer risk considerably, however switching to HPV based screening without changes in compliance is expected to reduce cancer risk by 12% compared to cytology based screening and any increased compliance has a stronger beneficial effect with HPV based screening than with cytology based screening.	1 underscreened, however favorable

Publication, Country	In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implement screening based on HPV testing identified? If yes, which barriers are these?	Concern category
[35] Goldhaber-Fiebert, 2008, USA	The authors argue that the full potential of the new screening strategies require that age-based guidelines will be followed. In addition efforts should be targeted to recruit and screen women with historically poor access to cervical cancer prevention	9 adherence 1 underscreened
[29],MSAC, 2014, Australia	The authors recommend strengthening adherence to screening with a “call-recall” system. The authors calculated that a call-recall system instead of only a reminder system will reduce cervical cancer incidence by 1% with an associated 2-3% relative increase in screening program cost. This system can only be implemented in an organized screening setting where all women are registered and receive an invitation to screening (“call”), where the attendance to and the result of the screening test is registered and in the absence of attendance a reminder (“recall”) is issued. “A systematic appraisal of evidence for invitation and recall systems was not undertaken in the evidence review, however a brief overview was provided. A number of studies (including RCTs, clustered RCTs and meta-analyses) supported the hypothesis that invitation systems would improve the uptake of screening (…). The meta-analyses found women who received invitations letters to attend screening had a significantly higher uptake of screening than women who received usual care or no invitation (relative rate 1.44 95%CI 1.24-1.52) (…).” The modelled analyses included a reduction in general practitioner (GP) consultations, recognizing that freeing these resources would allow them to be redeployed to relieve some capacity pressure through making available appointments for other services. A recent review by Dijkstra et al (2014) suggested the Meijer et al guidelines could be used to assess the clinical performance of a candidate test, relative to either HC2 or GP5+/6+ PCR by cross sectional clinical equivalence analysis in a screening setting. They reported that Roche cobas® 4800 and Abbott Real Time PCR have fulfilled the criteria provided in the guidelines with sensitivities ranging from between 100% and 95.8% and specificities from 96.7% to 92.3%. They suggested these assays have been clinically validated for primary HPV cervical screening. Quality Assurance System for Laboratories	15 call/recall 7 organized setting 22 central database 27 more free resources of GPs (favorable) 3 clinically validated tests 8 Quality Control
[33] Vijayaraghavan, 2010, Canada	Potential implementation problems could involve the available resources for colposcopy and biopsy, if a strategy is adopted that leads to increased colposcopy rates (e.g. HPV only)	28 colposcopy resources
[36], Vijayaraghavan, 2010, USA	No barriers were discussed	-
[77] Diaz, 2010, Spain	No barriers were discussed	-

Publication, Country	In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implement screening based on HPV testing identified? If yes, which barriers are these?	Concern category
[34], Kulasingam, 2009, Canada	No barriers were discussed	-
[78],Chuck, 2010, Alberta, Canada	Adherence to recommended screening strategies was mentioned as the most critical risk	9 adherence
[74] Mühlberger, 2008, Germany	No barriers to implementation were discussed, however auditing of screening programs is highly recommended by the authors to evaluate the history of women who develop cervical cancer to find out whether the failure of the screening program is due to non-attendance or other methodological weaknesses	10 monitoring and evaluation
[81] Dillner	"However, there are logistical challenges to implement HPV-based screening, such as the need to ensure that HPV tests are used at increased screening intervals and in the correct age groups, … the limited international standardization and quality assurance, and the need to optimize and evaluate the method switch in the real-life setting." "The necessary infrastructure to exploit the potential of HPV-based screening for improved cost-efficiency exists within organized, invitational screening programs. Piloting of HPV screening can be implemented by such programs, preferably as randomized healthcare policies." The authors raise the concern that 148 different HPV tests are available on the market (plus 44 variants). A method needs to be found to evaluate HPV assays with appropriate performance for screening Success factors: 1. Use standard and quality-assured HPV test 2. Tendered pricing 3. Do not invite too young women 4. Avoid unnecessary referrals of low-risk women with recently acquired HPV infections 5. Perform a pilot 6. Establish quality assurance system	9 adherence 8 Quality Control 10 monitoring and evaluation 7 organized setting 11 Pilot project 3 clinically validated tests 30 economy of scale
[79] Berkhof, 2010, Netherlands	Any potential strategy should be evaluated on detected number of high-grade lesions, costs and colposcopy rate computed from large cohort studies before implementation can take place.	11 Pilot Project
[31] van Rosmalen, 2012, Netherlands	One interesting feasibility aspect is the potential loss of women in follow up after a positive HPV test. This loss can be reduced by always taking the cervical smear in a way that both HPV test and cytology can be performed in the laboratory if the HPV test should be positive. Taking samples for both HPV and cytology will slightly increase the cost of initial sampling, so van Rosmalen et al simulated both options. The authors found that collecting the material for the first triage test during the visit for the primary test is more cost-effective than letting women return for a triage test after 2 weeks.	17 triage follow up

Publication, Country	In case that HPV testing is found to be clinically effective and cost effective: Are any potential barriers to implement screening based on HPV testing identified? If yes, which barriers are these?	Concern category
	It was not completely clear what the effect of dropouts in triage tests was. According to van Rosmalen if 10% of the women with a positive primary HPV test did not attend the triage tests primary cytology screening became the most cost-effective option, whereas according to De Kok with 90% attendance of triage HPV testing was still the most cost-effective option. Sampling for both the primary test and the triage test during the first screening visit should be taken into account if setting up a screening organization	
[80] de Kok, 2012, Netherlands	HPV based screening must, however, only be implemented in situations where screening is well controlled. “Implementing HPV screening in situations where screening is not well controlled carries risks that may be unacceptable. Frequent screening at a young age decreases the programme’s specificity given that every screening round adds to false positive test results (that is, the detection of non-progressive HPV infections or cervical intraepithelial neoplasia lesions), and screening at a young age detects many transient infections and abnormalities. “ In addition, HPV screening should be organized in such a way that the procedures are carried out in large centers to monitor the quality of the screening and to benefit from economies of scale. This is especially the case for HPV testing, which can be automated to a large extent, and where economies of scale will make a considerable difference to costs.	7 organized screening setting 9 adherence 29 large centers 30 economy of scale

18 Appendix 6: "EURONHEED checklists for the health economic studies"

Table 13: EURONHEED checklist for health economic studies

Page 1 of this table contains the questions of the EURONHEED checklist; pages 2 and 3 contain the ratings per publications. Questions in bold formatting and light blue background are relevant for the calculation of the transferability data score.

Question
Q1. Is the study question clearly stated?
Q2. Are the alternative technologies justified by the author(s)?
HT1. Is the intervention described in sufficient detail?
HT2. Is(are) the comparator(s) described in sufficient details?
SE1. Did the authors correctly specify the setting in which the study took place (e.g. primary care, community)?
SE2. Is(are) the country(ies) in which the economic study took place clearly specified?
P1. Did the authors correctly state which perspective they adopted for the economic analysis?
SP1. Is the target population of the health technology clearly stated by the authors, or when it is not done can it be inferred by reading the article?
SP2. Are the population characteristics described? (e.g. age, sex, health status, socioeconomic status, inclusion/ exclusion criteria)
SP3. Does the article provide sufficient detail about the study sample(s)?
SP4. Does the paper provide sufficient information to assess the representativeness of the study sample with respect to the target population?
M1. If a model is used is it described in detail?
M2. Are the origins of the parameters used in the model given?
E1. If a single study is used is the study design described (sample selection, study design, allocation, follow-up)?
E2. If a single study is used are the methods of data analysis described (intention to treat/per protocol or observational data)?
E3. If based on a review/synthesis of previous published studies, are review methods described (search strategy, inclusion criteria, sources, judgment criteria, combination, investigation of differences)?
E4. If based on opinion, are the methods used to derive estimates described?
E5. Have the principal estimates of effectiveness measures been reported?/ Is the level of reporting of the effectiveness results adequate
E6. Are the side-effects or adverse effects addressed in the analysis?
E7. Does the article provide the results of a statistical analysis of the effectiveness results?
B1. Do the authors specify any summary benefit measure(s) used in the economic analysis?
B2. Do the authors report the basic method of valuation of health states or interventions?
B3. Do the authors specify the source(s) of health states (e.g. specific patient population or the general public)?
B4. Do the authors specify the valuation tool used?
B5. Is the level of reporting of benefit data adequate (incremental analysis, statistical analyses)?
C1. Are the cost components/items used in the economic analysis presented?
C2. Are the methods used to measure costs components/items provided?
C3. Are the sources of resource consumption data provided?
C4. Are the sources of unit price data provided?
C5. Are unit prices for resources given?
C6. Are costs and quantities reported separately?
C7. Is the price year given?
C8. Is the time horizon given for each element of the cost analysis?
C9. Is the currency unit reported?
C10. Is a currency conversion rate given?
C11. Does the article provide the results of a statistical analysis of cost results?
D1. Was the summary benefit measure(s) discounted?
D2. Were the cost data discounted?
D3. Do the authors specify the rate(s) used in discounting costs and benefits?
D4. Were discounted and not discounted results reported?
S1. Are quantitative and/or descriptive analysis conducted to explore variability from place to place?
O1. Did the authors discuss caveats regarding the generalizability of their results?
Quality Data Score
Transferability Data Score

Study	USA Huh	Belgium Arbyn	Australia MRCA	NL deKok	Germany Sroczynski	NL van Rosmalen	UK Kitchener	US Vijaya-raghavan
Q1	yes	yes	yes	yes	Yes	yes	yes	yes
Q2	yes	yes	yes	yes	yes	yes	yes	yes
HT1	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
HT2	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
SE1	yes	yes	yes	yes	yes	yes	yes	yes
SE2	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
P1	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
SP1	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
SP2	yes	yes	yes	yes	yes	yes	yes	yes
SP3	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
SP4	yes	yes	N/A	yes	P	yes	N/A	N/A
M1	yes	yes	P	yes	yes	P	P	yes
M2	yes	yes	yes	yes	yes	yes	P	yes
E1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
E2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
E3	N/A	P	N/A	N/A	P	N/A	N/A	N/A
E4	N/A	yes	N/A	N/A	P	N/A	N/A	N/A
E5	**yes**	**yes**	**yes**	**partially**	**yes**	**yes**	**yes**	**yes**
E6	yes	yes	yes	partially	No/NI	P	yes	No/NI
E7	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
B1	yes	yes	yes	yes	yes	yes	yes	yes
B2	yes	N/A	yes	yes	N/A	yes	No/NI	yes
B3	yes	N/A	yes	partially	N/A	P	P	yes
B4	yes	N/A	yes	partially	N/A	P	P	yes
B5	**yes**	**yes**	**P**	**yes**	**yes**	**yes**	**P**	**yes**
C1	**P**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
C2	yes	yes	yes	partially	yes	yes	yes	yes
C3	yes	yes	yes	partially	yes	P	yes	yes
C4	yes	yes	yes	partially	yes	P	yes	yes
C5	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
C6	**P**	**P**	**P**	**partially**	**P**	**P**	**P**	**P**
C7	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
C8	yes	P	P	partially	P	P	P	yes
C9	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
C10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
C11	yes	yes	yes	yes	yes	yes	yes	yes
D1	yes	yes	yes	yes	yes	yes	yes	No/NI
D2	yes	yes	yes	yes	Yes	yes	yes	No/NI
D3	yes	yes	yes	yes	yes	yes	yes	N/A
D4	P	yes	P	yes	yes	yes	P	N/A
S1	**P**	**No/NI**	**No/NI**	**yes**	**P**	**No/NI**	**yes**	**P**
O1	**P**	**P**	**P**	**yes**	**P**	**yes**	**yes**	**P**
Q Score	0.93	0.91	0.89	88%	0.87	0.86	0.86	0.86
T Score	0.87	0.87	0.83	91%	0.90	0.90	0.93	0.90

Study	Sweden Bistoletti	Norway Burger	USA Goldha-ber-Fiebert	Canada Kulasingam	Canada Chuck	Spain Diaz	Canada Vijayara-ghavan	Italy Accetta
Q1	yes	yes	yes	yes	yes	yes	yes	yes
Q2	yes	yes	P	yes	P	yes	P	P
HT1	**no/NI**	**yes**	**yes**	**P**	**yes**	**yes**	**P**	**no/NI**
HT2	**no/NI**	**yes**	**yes**	**yes**	**yes**	**yes**	**P**	**no/NI**
SE1	yes	P	yes	P	P	yes	yes	P
SE2	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
P1	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**P**
SP1	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
SP2	yes	yes	yes	P	yes	yes	P	yes
SP3	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
SP4	yes	P	N/A	yes	P	P	P	N/A
M1	yes	P	P	P	yes	P	P	yes
M2	yes	yes	yes	yes	yes	yes	yes	yes
E1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
E2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
E3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
E4	N/A	No/NI	N/A	N/A	N/A	N/A	No/NI	P
E5	**yes**	**P**	**yes**	**P**	**No/NI**	**No/NI**	**yes**	**yes**
E6	No/NI	P	No/NI	P	P	P	P	No/NI
E7	**yes**	**P**	**yes**	**P**	**P**	**No/NI**	**P**	**No/NI**
B1	yes	yes	yes	yes	yes	yes	yes	yes
B2	N/A	N/A	P	yes	yes	N/A	P	P
B3	N/A	N/A	No/NI	yes	yes	N/A	P	No/NI
B4	N/A	N/A	No/NI	yes	yes	N/A	P	No/NI
B5	**P**	**P**	**yes**	**P**	**No/NI**	**P**	**P**	**yes**
C1	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
C2	yes	yes	yes	yes	yes	yes	P	yes
C3	yes	yes	yes	yes	yes	yes	P	yes
C4	yes	yes	yes	yes	yes	yes	yes	yes
C5	**yes**	**yes**	**yes**	**yes**	**No/NI**	**yes**	**yes**	**yes**
C6	**P**	**P**	**P**	**P**	**P**	**P**	**P**	**P**
C7	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
C8	yes	P	P	P	yes	P	yes	P
C9	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
C10	No/NI	yes	N/A	N/A	N/A	N/A	N/A	N/A
C11	P	P	yes	yes	yes	No/NI	yes	No/NI
D1	yes	yes	yes	yes	yes	yes	yes	yes
D2	yes	yes	yes	yes	yes	yes	yes	yes
D3	yes	yes	yes	yes	yes	yes	yes	yes
D4	yes	P	P	P	No/NI	P	P	P
S1	**P**	**P**	**P**	**yes**	**No/NI**	**No/NI**	**No/NI**	**No/NI**
O1	**yes**	**yes**	**P**	**P**	**yes**	**P**	**yes**	**No/NI**
Q Score	0.82	0.80	0.80	0.78	0.78	0.76	0.73	0.65
T Score	0.77	0.83	0.90	0.80	0.67	0.70	0.77	0.60

19 Appendix 7: "Transferability Analysis for the health economic studies"

Table 14: Transferability analysis of health economic studies to the Swiss health system

Study	**Transferability Summary**
[35] Goldhaber-Fieber, 2008, USA	**Transferability is potentially possible. A comparator was used that reflects Swiss screening recommendations. Follow up of CIN1 may be slightly different in that in the US CIN1 will be followed up by surveillance until negative, while in Switzerland CIN1 is recommended for treatment if persistent. HPV prevalence seems to be slightly lower than in Switzerland, which may slightly favor HPV based testing (with lower prevalence a more sensitive test is of advantage).**
Transferability question	Analysis of the study
Was a comparator used that is relevant for the Swiss setting?	Yes, 3-yearly cytology with HPV triage was modelled.
Sensitivity of cytology	70% for CIN1 and 80% for CIN2+, this was varied in the sensitivity analysis between 18.6-99% If the sensitivity of the cytological evaluation was reduced by more than 15% (e.g., below 70% for CIN2,3), then HPV DNA testing with cytology triage became increasingly attractive (see the Supplementary Appendix, pp. 21,120, available online).
Sensitivity of HPV	83% for CIN2+, this was varied in the sensitivity analysis between 70 -85% Changes in the specificity of HPV DNA testing were more influential than changes in test sensitivity. For example, compared with cytology-based strategies, HPV DNA testing with cytology triage every 5 years remained an efficient strategy even when the sensitivity for CIN2, 3 was as low as 70%. In contrast, when the specificity of HPV DNA testing was less than 85%, cytology-based screening with HPV DNA testing when ASC-US was detected was preferred (see the Supplementary Appendix, pp. 23,125,126, available online).
Viewpoint of the analysis	Health Care Payer perspective plus some societal costs were included (direct medical costs, patient time and transport cost for screening, diagnostic follow up and cancer treatment)
Do treatment options compare to current clinical practice in Switzerland?	Women with histologically confirmed CIN1 are not treated but are monitored every 6 – 12 months until they have three negative screening test results. In comparison in Switzerland CIN1 is recommended for treatment if persistent
Is there any hint for a different base line risk of the populations?	hrHPV prevalence in this model seems to be slightly lower than in Switzerland (compared to de Vuyst), while cervical cancer incidence in the US has been reported slightly higher (2007–2011 US age-adjusted incidence of 7.8 per 100,000 reported by the SEER (acc. to Huh 2015) compared to 5.4 in Switzerland
Do the screening setting or attendance rates influence the result??	US screening is opportunistic with different ethnic groups having or using different access to health care resources. Adherence rates were varied to reflect observations from different ethnic groups. All groups will have an incremental benefit of switching to the recommended HPV based testing. The effect being higher with increasing adherence levels to new recommendations

Study	Transferability Summary
[32] **Burger, 2012, Norway**	**Transferability is potentially possible.** **The screening strategy is similar as in Switzerland with the exception that LSIL is only followed up with colposcopy in Norway, if persistent and that ASC-US and LSIL are followed up with HPV and cytology cotesting. However the strategies are still comparatively close.** **In this model women were switched to HPV testing at 31 years and HPV positive results were followed with cotesting triage.**
Transferability question	Analysis of the study
Was a comparator used that is relevant for the Swiss setting?	The current Norwegian screening strategy is 3 yearly cytology with cotesting triage for ASC-US or LSIL after 6 months. Women with HSIL are referred directly to colposcopy/ biopsy. This strategy is similar to the current Swiss recommendations with the exception that in Switzerland with LSIL immediate colposcopy is recommended Theoretically due to the stricter follow up the Swiss cytology strategy could be more sensitive than the Norwegian strategy. On the other hand comparatively high sensitivities of cytology based testing to detect CIN2+ were assumed in the model. Therefore the differences in the strategy seem negligible.
Sensitivity of cytology	Sensitivity of cytology was 70% to detect CIN1 and 80% to detect CIN2+ Assuming lower sensitivities of 50% or 40% made an HPV based strategy with 5-yearly testing the optimal strategy with colposcopy after only 1 repeated HPV+/Cyt- result after 6 months (instead of 4-yearly with 12 months before colposcopy)
Sensitivity of HPV	Sensitivity and specificity of the HPV test for the presence or absence of HPV was assumed 100%
Viewpoint of the analysis	In addition to direct medical costs indirect medical costs (patients' transport costs) and some social costs (patient time translated into cost for productivity loss) for screening, diagnostic follow up and treatment was calculated.
Do treatment options compare to current clinical practice in Switzerland?	Treatment options are not described in detail; however costs for CIN1 treatment were shown indicating that this stage is eligible for treatment in the Norwegian context. In comparison in Switzerland CIN1 is recommended for treatment if persistent. On the other hand in Norway LSIL is not immediately followed up with colposcopy, but only if persistent. If in this case CIN1 is detected, this may also be a persistent histological finding.
Is there any hint for a different base line risk of the populations?	No data were available for the prevalence of hrHPV. Incidence and mortality rates are 9.5 and 1.7 per 100 000 women-years, respectively (Cancer Registry of Norway, 2011) compared to 5.4 and 1.4 in Switzerland
Do the screening setting or attendance rates influence the result??	Norway has an invitational system. In the base case 100% compliance with all recommendations was assumed to compare maximum possible benefits of each strategy In addition in the sensitivity analysis 2 scenarios were included in which 15 or 20% never attend and 70% comply with recommendations and the rest screens less frequently (1 year later) than recommended. Potentially scenario 2 is closest to the Swiss situation. The strategy with HPV testing every 4 years remained to be the best case

Study	Transferability Summary
[30, 60] Sroczynski, 2010, 2011, Germany	**Despite the differences between the German and the Swiss screening approaches (details see below) the results may be transferable to the Swiss setting. As a conservative assumption the base case with higher sensitivities for cytology testing would be taken as transferable.**
Transferability question	Analysis of the studies
Was a comparator used that is relevant for the Swiss setting?	3-yearly Pap test was modelled; however follow up of positive Pap tests was slightly different. While Swiss recommendations indicate colposcopy for LSIL and HSIL, in the German model more than 50% of the HSIL was followed by retest with either cytology or HPV or a combination of both. For LSIL retesting was done for more than 76% of the women instead of colposcopy. 63% of ASC-US results receive repeat Pap testing and 26% HPV or cotesting, the rest is referred to colposcopy. In the "HPV" strategy, a positive HPV test was followed up with Pap triage in 43% of the cases, 23% were referred to colposcopy, the rest retested with HPV or cotesting. As in Switzerland some variability in adherence to recommendations will probably exist, this strategy may still be a close comparator to the Swiss health system. In the HPV with Pap triage or cotesting strategies a finding of HPV and Pap positivity was not always followed up with colposcopy, but depending on the severity of the Pap finding. With HSIL referral to colposcopy or immediate treatment was done in 63% of the cases, with LSIL in 44% and ASC-US 20%. This is a less stringent follow up of positive test results than in other models in other countries and less stringent than recommended for Switzerland. Potentially therefore both the comparator strategy in Germany as well as the modelled HPV based strategy may be less sensitive than possible. As this may affect both the comparator and the HPV based strategy, the result of this study is still relevant.
Sensitivity of cytology	Base case 47% for CIN1 and 72% for CIN3+, "German case" 42% for CIN1 and 46% for CIN3+
Sensitivity of HPV	Base case 81% for CIN1 and 98% for CIN3+, "German case" 81% for CIN1 and 97% for CIN3+
Viewpoint of the analysis	Third party payer, direct medical costs in the context of diagnosis, therapy and follow-up care of cervical cancer and its precursor states
Do treatment options compare to current clinical practice in Switzerland?	Treatment recommendations in Germany and Switzerland are similar in that the age of affected women is taken into account to take a decision for immediate treatment of precancerous lesions or surveillance. From the discussion in the German publication it is indicated that CIN2 is less often treated but more often referred to surveillance, than e.g. in US studies where treatment was always indicated, however the recommendations involve judgment of the responsible physicians and actual treatment frequencies were not reported. Variation of treatment cost did not have a relevant impact on the results.
Is there any hint for a different base line risk of the populations?	No data were available in Germany for age related HPV prevalence. Incidence of cervical cancer is about 9-10/100'000 in Germany compared to 4.5 in Switzerland. This result may be due to differences in the screening strategies and not necessarily reflects different background risk.
Do the screening setting or attendance rates influence the result??	What attendance rates were modelled? An average screening adherence of only 55% was assumed in the base case and in the sensitivity analysis varied between 0% and 100%. The relative effectiveness of the strategies did not change with different adherence rates

Study	Transferability Summary
[75] Bistoletti, 2008, Sweden	**It is unclear whether the findings of this study are transferable to the Swiss setting. The sensitivity of cytology testing in Sweden may be lower than in Switzerland, which would favor HPV testing in the study. The model started screening only at 32 years, leading to a higher background risk at the start of screening. Only the primary screening test is described, not the follow up after a positive primary screening test. 3 HPV based tests in a woman's life were more effective and less expensive than 3 yearly cytology based screening between 32 and 50 years, afterwards 5 yearly cytology, however it is unclear how this strategy would compare to the Swiss 3-yearly cytology with HPV triage.**
Transferability question	Analysis of the studies
Was a comparator used that is relevant for the Swiss setting?	Cytology screening at 32 to 50 in 3-yearly intervals, afterwards 5 yearly was the comparator, however as an important limitation only the primary screening test is described, not the follow up after positive results. Starting screening only at age 32 will lead to a higher background risk at start of screening
Sensitivity of cytology	Invasive cancer if Cyt pos: p=0.0017, Invasive cancer if Cyt neg: p=0.0001, Normal if Cyt neg: p=0.9999 Sensitivity and specificity of cytology may be lower in Sweden than in other countries incl. Switzerland as in Sweden more cytology samples were read as normal, which in other countries (UK, US) were read as ASC-US. This could point at a low sensitivity of cytology which would make HPV based screening more favorable in comparison.
Sensitivity of HPV	For cotesting the assumptions were: Invasive cancer if Cyt pos or HPV pos: p=0.0017, CIN2-3 if Cyt pos or HPV pos: 0.18, Invasive cancer if Cyt neg & HPV neg: p= 0.00008 All data were based on Swedish data of the Swedescreen study or earlier publications
Viewpoint of the analysis	Provider/health service perspective
Do treatment options compare to current clinical practice in Switzerland?	Treatment was only indicated for CIN2 and 3, and CIN 1 is under surveillance with cytological screening, while in Switzerland also CIN1 will be treated if persistent.
Is there any hint for a different base line risk of the populations?	HPV prevalence in women between 32 and 38 years is 7.1% in Sweden (deVuyst 2009). Prevalence in that age group was found higher in a study in Switzerland (10- 15%) (deVuyst 2009). The ASR of cervical cancer incidence in Sweden is 7.4 vs 5.4 /100'000 women in Switzerland)
Do the screening setting or attendance rates influence the result??	50% organized, 50% opportunistic screening was assumed with 75% attendance rate at each screening cycle and 100% adherence to follow up.

Study	Transferability Summary
[2] Kitchener, 2014, UK	**Transferability is limited as the closest comparator of cytology with HPV triage was only modelled slightly later with screening (25 years, compared to 21 in Switzerland) and women of 50-64 years are only tested every 5 years vs 3 yearly in Switzerland. In Switzerland screening is recommended until the age 70. Therefore the Swiss current screening may be more effective and more expensive than this comparator screening.** **Age specific incidence rates for cervical cancer in young women are much higher in the UK than in Switzerland.**
Transferability question	Analysis of the study
Was a comparator used that is relevant for the Swiss setting?	The closest comparator is a 3-yearly cytology screening (LBC) with HPV triage (current screening practice) in women of 25-49 years and 5-yearly cytology screening for women 50-64 years
Sensitivity of cytology	The LBC positivity rate for CIN2+ was estimated at 77% with ASC-US and 70% with LSIL result and for CIN3+ with 76% (ASC-US) and 70 % (LSIL)
Sensitivity of HPV testing	HPV was assumed to give positive results for 96% of CIN2 and 96% for CIN3+
Viewpoint of the analysis	The economic evaluation of primary HPV screening in England took a health services perspective, taking into account the health services costs associated with population-based screening, management, diagnosis, and follow-up and treatment of CIN and invasive cancer. Cost for organized screening was added to the calculations. This is different from current screening in Switzerland, however, a scenario that may become relevant in Switzerland in the future.
Do treatment options used in the model compare to current clinical practice in Switzerland?	In the UK women with histologically confirmed CIN1 are not treated but are monitored every 6 – 12 months. The authors assume that a small part of CIN1 will be treated along with CIN2+. In comparison in Switzerland CIN1 is recommended for treatment if persistent
Is there any hint for a different base line risk of the populations?	hrHPV prevalence in the UK is higher than in Switzerland until the age of 40 and afterwards similar or slightly lower [62]. Data from the HART study were used as basis as they come from 5 cities. Here prevalence in the age group of 30-69 is 7.1% vs 9.4% in Switzerland. Differences have been reported between different areas in the UK ranging from 5% in South Wales to 10% in Manchester for the age group of 30 to 69 [62]. Age specific cervical cancer incidence in the UK is much higher than in Switzerland at age 25-35 (around 17/100'000 in the UK versus less than 8 in Switzerland in this age group).
Does the screening setting influence the result? What attendance rates were modelled?	England cervical cancer screening organized different to the Swiss system. Therefore in this model the cost of the screening organization is added to the calculation. Attendance at routine screening was assumed to be around 85% which may be higher than in Switzerland. Attendance rates of follow up tests was calculated more conservatively than in many other studies with 80-85% in the base case (and modelled in the sensitivity analysis between 60 and 100%). Attendance at follow up tests is important especially for HPV+/cyt- women

Study	Transferability Summary
[37] Huh, 2015, USA	**Transferability is limited in that all strategies started at 30 years which leads to higher baseline risk at start of screening. However under the assumption that a strategy in Switzerland may involve cytology screening for women up to the age of 30 and only afterwards the strategy would switch, the comparison of strategies after the age of 30 is still of interest. Different to the recommendations in Switzerland no treatment cost for CIN1 and CIN2 was calculated in this study.**
Transferability question	Analysis of the study
Was a comparator used that is relevant for the Swiss setting?	Yes, 3-yearly cytology testing with HPV triage, however all strategies start only at 30 years (leading to higher baseline risk at start of screening)
Sensitivity of cytology	Sensitivity to detect CIN3+ cytology 56%
Sensitivity of HPV	HPV with cytology triage: 52%, HPV with 16/18 genotyping: 72%, cotesting 56%
Viewpoint of the analysis	US healthcare payers perspective
Do treatment options compare to current clinical practice in Switzerland?	No treatment cost for CIN1 and CIN2 were calculated. The authors argue that “Since approximately 90 % of CIN 1 and 88 % of CIN 2 cases regress within 1 year [31, 32], the model accounted only for sensitivity in detecting incident and persistent cases of CIN 3.” It was not discussed, how women with CIN1 and CIN2 should be followed up and it is unclear how the costs for this were taken into account in the model. In comparison in Switzerland CIN2 is recommended for treatment and CIN1 is treated if persistent. Since disutilities were assigned to CIN1 and CIN2 QALYs as effectiveness measure take increased detection of CIN1 and CIN2 into account
Is there any hint for a different base line risk of the populations?	hrHPV prevalence in women of 30-60 years in the US seems to be slightly lower but close being 8.5% vs 9.4% in Switzerland [37, 62]. Incidence of cervical cancer is 7.8/100’000 [37] compared to 5.4 in Switzerland Based on HPV prevalence the background risk may be similar
Do the screening setting or attendance rates influence the result??	The model assumed “that all women complied with scheduled screening visits as well as recommendations for colposcopy and biopsy.” Thereby the model compares the maximum possible effect of all strategies. Other studies have varied the attendance rates in their sensitivity analyses and found that this did not change the relative effectiveness of strategies, however higher attendance rates led to higher effectiveness and higher ICERs

Study	Transferability Summary
[28] Arbyn, 2015, Belgium	**Transferability is likely.** **The study included a comparator that reflects Swiss screening recommendations. Like in Switzerland all CIN stages seem to be eligible for treatment. HPV prevalence and cervical cancer incidence are slightly higher in Belgium than in Switzerland. However according to [80] higher HPV prevalence favor cytology based screening, so the case could be even more favorable in the Swiss environment.**
Transferability question	Analysis of the study
Was a comparator used that is relevant for the Swiss setting?	Yes, cytology screening with HPV triage was modelled, with an algorithm that reflects Swiss recommendations
Assumed sensitivity of cytology	51% for CIN2 and 49% for CIN3+ (age group 35-49, higher sensitivities in older women of around 80%)
Assumed sensitivity of HPV testing	95% for CIN2 and 95% for CIN3+ (age group 35-49, higher sensitivities in older women of around 99-100%)
Viewpoint of the analysis	The economic evaluation was undertaken from the perspective of the health care payer. Costs included were direct medical costs paid out of the health care budget and the patients' out-of-pocket expenses for health care. Societal costs such as productivity losses and direct non-health care costs such as personal travel expenses were not accounted for.
Do treatment options used in the model compare to current clinical practice in Switzerland?	Exact treatment was not described. Cost data were included for CIN 1,2 and CIN3 indicating that all precancerous lesions have a planned treatment pathway
Is there any hint for a different base line risk of the populations?	hrHPV prevalence in women of 30-60 years in Belgium is 12.5 vs 9.4% in Switzerland [62]. The incidence of cervical cancer is 9.7/100'000 (8.1 in 2012 acc. to [28])
Does the screening setting influence the result? What attendance rates were modelled?	The base case assumed a 60% 3 year participation rate (40-80%) increasing the participation at cytology screening to 80% (instead of 60% in the base) decreases the incidence of cervical cancer and reduces the incremental number of LY saved by HPV screening by 20% (from 2878 to 2312 LY gained). Though slightly c reduced, HPV screening still results in net savings (€14.4 million instead of €14.8 in the base case), such that HPV screening remains a dominant option. The finding that HPV testing is more effective at a lower price was robust to participation rates. It is likely that in Switzerland too a participation rate between 60 and 80% can be reached.

Study	**Transferability Summary**
[76] **Accetta, 2010, Italy**	**The study did not describe in detail the follow up of triage tests. Under the assumption that the strategy cytology with HPV triage is similar to the current Swiss recommendations transferability of the results may be considered.**
Transferability question	Analysis of the study
Was a comparator used that is relevant for the Swiss setting?	As a limitation of this study the follow up of triage tests is not described. It can be assumed that cytology with HPV triage from 25-65 years represents a strategy that is similar to the current Swiss recommendation
Assumed sensitivity of cytology	sensitivity for low grade lesions is assumed 70%, high grade lesions 80% and for cancer 100%
Assumed sensitivity of HPV testing	According to the publication a sensitivity of the HPV test for hrHPV was assumed 96%. However it looks inconsistent with data from other studies that the sensitivity of the HPV test for hrHPV is only as low as 96% (with reference to Ronco 2006 and 2008) and specificity only 94%. Arbyn (2015) assigns with reference to Ronco 2006 a sensitivity of the HPV test of 96% to detect CIN3+ (not just hrHPV)
Viewpoint of the analysis	Authors did not state the perspective taken, however from the costs taken into account the perspective seems to be that of the health system including direct medical costs
Do treatment options used in the model compare to current clinical practice in Switzerland?	Treatment is not described; however costs for CIN1 treatment were not shown indicating that this stage is not eligible for treatment in the model. In comparison, in Switzerland CIN1 is recommended for treatment if persistent.
Is there any hint for a different base line risk of the populations?	hrHPV prevalence is comparable. The incidence rate for cervical cancer is 9.5 per 100 000 women-years, (Cancer Registry of Italy, 2011) compared to 5.4 in Switzerland.
Does the screening setting influence the result? What attendance rates were modelled?	Italy with invitational system, no further details Average compliance with the screening schedule was assumed 70.9% (based on Italian statistics of 2005). Three groups were defined: Women who never undergo screening (20%), women who always undergo screening (44%) and women for whom the compliance increases with age (36%)

Study	Transferability Summary
[29] MSAC, 2014, Australia	**Transferability is limited as the closest comparator of cytology with HPV triage was only modelled slightly later with screening (25 years, compared to 21 in Switzerland) and women of 50-64 years are only tested every 5 years vs 3 yearly in Switzerland. In Switzerland screening is recommended until the age 70. Therefore the Swiss current screening may be more effective and more expensive than this comparator screening.**
Transferability question	Analysis of the study
Was a comparator used that is relevant for the Swiss setting?	The closest comparable strategy modelled was 3-yearly screening with LBC and HPV triage for women aged 25-49 and 5-yearly screening for women aged 50-64.
Sensitivity of cytology	With LSIL taken as threshold the sensitivity was assumed 74% for CIN2+ and 76% for CIN3+
Sensitivity of HPV testing	96% sensitivity for CIN2+ and 98% sensitivity for CIN3+
Viewpoint of the analysis	A health service perspective was taken
Do treatment options used in the model compare to current clinical practice in Switzerland?	CIN2 and 3 are treated, CIN1 is put to surveillance, whereas in Switzerland CIN1 is treated if persistent
Is there any hint for a different base line risk of the populations?	Only graphical presentations could be compared. In these hrHPV prevalence in the Australian model seems to be slightly lower than in Switzerland (compared to de Vuyst), while cervical cancer incidence in Australia seems similar or slightly higher compared to Switzerland
Does the screening setting influence the result? What attendance rates were modelled?	Screening in Australia is organized The authors found that it makes a difference, whether reminder systems are used or call/recall set ups. A “Call / Recall” instead of “Reminder” system will improve adherence to recommended screening intervals and reduce cervical cancer incidence by 1% with an associated 2-3% relative increase in screening program cost.

Study	**Transferability Summary**
[33] Vijayaraghavan, 2010, Canada	**3 yearly cytology testing with HPV triage was used as comparator. Young women were screening with Pap testing and were switched to different screening strategies at the age of 30 years, As a downside of this study it was impossible to retrieve from the study author the supplementary material which described treatment options and the sensitivity analysis.**
Transferability question	Analysis of the study
Was a comparator used that is relevant for the Swiss setting?	3-yearly cytology testing with HPV triage was modelled
Assumed sensitivity of cytology	33% sensitivity for CIN1+, 59% sensitivity for CIN2+ (CCCaST)
Assumed sensitivity of HPV testing	71% for CIN1+, 98% for CIN2+
Viewpoint of the analysis	We adopted a health care payer perspective and as such included direct medical costs
Do treatment options used in the model compare to current clinical practice in Switzerland?	Treatment options were only described in the supplement material, which was impossible to obtain up to now
Is there any hint for a different base line risk of the populations?	hrHPV prevalence was similar in women of 30-39 years and afterwards lower than in published values for Switzerland [62]. Cervical cancer incidence seems to be slightly higher than in Switzerland compared to Canadian incidence graphs presented in [34]
Does the screening setting influence the result? What attendance rates were modelled?	In the base case 100% adherence and compliance was assumed. Attendance rates were varied in sensitivity analyses, however did not change the rank order between strategies (e.g. 16% never screened, 70% as recommended, 18% missing follow-up colposcopies) More details on this sensitivity analysis were supposedly described in supplements, which were impossible to obtain up to now

Studies that don't have a comparator relevant for the Swiss health care system

Study	**Transferability Summary**
[36] **Vijayaraghavan, 2010, USA**	**Transferability analysis impossible – no comparator equivalent to Swiss cervical cancer screening used**
Transferability question	Analysis of the study
Was a comparator used that is relevant for the Swiss setting?	Strategies compared included 2-yearly LBC, 2-yearly LBC with HPV triage, 3-yearly HPV with LBC triage, 3-yearly co-screening and 3-yearly co-screening with HPV genotyping and HPV with 16/18 genotyping As no comparator was used that was equivalent to the Swiss recommended screening of 3-yearly cytology with HPV triage, no detailed transferability analysis was done

Study	**Transferability Summary**
[34] Kulasingam, 2009, Canada	**Transferability analysis impossible – no comparator equivalent to Swiss cervical cancer screening used**
Transferability question	Analysis of the study
Was a comparator used that is relevant for the Swiss setting?	Unfortunately no comparator that directly reflects Swiss recommendations was used. Pap with HPV triage was only modelled with 1-yearly frequency 3-yearly Pap testing was only modelled with Pap triage therefore no further transferability analysis was done

20 Appendix 8: "Costs and cost effectiveness values in CHF by adaptation to purchasing power parities"

The following table shows the deduction of test costs and cost effectiveness results in CHF by adaptation to purchasing power parities according to the description in the methods chapter 5.4.7

Table 15: Deduction of cost of testing and cost effectiveness values in CHF by adaptation of purchasing power parities

Study	**Summary**[12]
[30, 60] Sroczynski, 2010, 2011, Germany	**In the base case with higher sensitivities for cytology testing, 3-yearly HPV based screening (where most of the HPV positive samples were followed up with cytology triage) at a cost of 101 CHF for HPV testing (thereof 42 CHF for the HPV assay) resulted in an ICER of 17'450 CHF/LYG.**
Deduction of costs and ICERs into CHF by adaption to purchasing power parities and inflation to 2015	Strategy — ICER (CHF 2015/LYG) no screening — - Pap 5y — 5'041 Pap 3y — 13'766 HPV 3y — 17'450 HPV 2y — 55'064 HPV + Pap-Triage, 2y — 181'673 HPV 1y — 301'496 In a scenario, where Pap test sensitivity was lower based on German studies all Pap test based strategies were dominated and 5 yearly HPV based testing was cost effective at 6'786 CHF/LYG (against no screening) and 3-yearly HPV based testing at 11'827 CHF/LYG (against 5 yearly HPV based testing)
Assumed cost for cytology in 2015 CHF	71 CHF
Assumed cost for HPV testing in 2015 CHF	101 CHF thereof 42 CHF for the HPV test

[12] Strategies are shown in order of their effectiveness. ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study.

Study	Summary
[75] Bistoletti, 2008, Sweden	**It is unclear whether the findings of this study are transferable to the Swiss setting. Sensitivity of cytology testing in Sweden may be lower than in Switzerland, which would favor HPV testing in the study. The model started screening only at 32 years, leading to a higher background risk at the start of screening. Only the primary screening test is described, not the follow up after a positive primary screening test. 3 HPV based tests in a woman's life were more effective and less expensive than 3 yearly cytology based screening between 32 and 50 years, afterwards 5 yearly cytology, however it is unclear how this strategy would compare to the Swiss 3-yearly cytology with HPV triage.**
Deduction of costs and ICERs into CHF by adaption to purchasing power parities and inflation to 2015	Transferability is limited. Only the primary screening test is described, not the follow up after positive results. All screening started only at 32 years. Three HPV based tests in a woman's life were more effective and less expensive than 3 yearly cytology based screening between 32 and 50 years, afterwards 5 yearly cytology.
Assumed cost for cytology in 2015 CHF	45 CHF
Assumed cost for HPV testing in 2015 CHF	90 CHF

Study	Summary[13]
[2] Kitchener, 2014, UK	**Under the assumption of the UK setting and with cytology test prices of 11 CHF if negative, 32 CHF if positive and an HPV test price of 20 CHF the costs for the different strategies translates into ICERs between 32'171 CHF for HPV with genotyping for HPV16/18 and 24 months follow up of HPV+/cyt- women, 42'895 for HPV with LBC triage and genotyping for HPV 16/18 for women initially HPV+/cyt- and 64'342 CHF for HPV with genotyping for HPV16/18 and 12 month follow up of HPV+/cyt- women.**
Deduction of costs and ICERs into CHF by adaption to purchasing power parities and inflation to 2015	CP= Current practice S3= HPV with HPV 16/18 genotyping (if HPV 16/18 positive refer to colposcopy, if positive for other hrHPV cytology triage) S1= HPV with LBC triage S2= HPV with LBC triage (immediate) and HPV 16/18 genotyping (after 12 months) for women who were HPV pos/ cyt neg S4= Cotesting (with HPV 16/18 genotyping after 24 months for women who were HPV pos/cyt neg) S3= HPV with HPV 16/18 genotyping (if HPV 16/18 positive refer to colposcopy, if positive for other hrHPV cytology triage) Strategy code: CP; S1 24m 30y; S1 24m 35y; S2 24m 35y; S2 24m 25y; S2 24m 30y; S3 24m 25y; S1 12m 25y; S2 12m 25y; S4 12m 25y; S3 12m 25y ICER CHF/LYG: Dominated; Dominated; Dominated; Dominated; 21'447; Dominated; 32'171; 64'342 (dominated, but lower colposcopy rates); 42'895 (against S3 24m 25y); dominated; 64'342 (against S2 12m 25y)
Assumed cost for cytology in 2015 CHF	11 CHF if negative, 32 CHF if positive
Assumed cost for HPV testing in 2015 CHF	20 CHF

[13] Strategies are shown in order of their effectiveness. ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study.

Study	Summary[14]
[37] Huh, 2015, USA	**With a price of cytology testing of 37 CHF and 62 CHF for HPV testing (including genotyping for HPV 16/18) 3-yearly screening with HPV 16/18 genotyping had an ICER of 10'000 CHF /QALY. The authors calculated that this strategy would still be the most cost effective one, up to a price of 193 CHF, resulting in an ICER of 62'193 CHF/QALY.**
Deduction of costs and ICERs into CHF by adaption to purchasing power parities and inflation to 2015	ICER CHF 2015$/QALY cytology + HPV triage = baseline cytology + HPV cotest = dominated HPV + cytology triage = dominated HPV + 16/18 genotyping = 10'001
Assumed cost for cytology in 2015 CHF	37 CHF
Assumed cost for HPV testing in 2015 CHF	62 CHF including HPV genotyping for HPV 16/18 in the base case (however the HPV16/18 genotyping strategy was cost effective with an ICER below 65'222 CHF up to an HPV test price of 193 CHF)

Study	Summary[15]
[28] Arbyn, 2015, Belgium	**At the assumptions taken in the study and at a price of 35 CHF for cytology (52 CHF if a second reading is necessary) and 56 CHF for the HPV assay, 5 yearly HPV testing dominated 3 yearly cytology. If an HPV test price of 92 CHF was assumed the strategy HPV with cytology triage had an ICER of 6'862 CHF /LYG**
Deduction of costs and ICERs into CHF by adaption to purchasing power parities and inflation to 2015	In the base case with 57 CHF for the HPV test, 5 yearly HPV testing dominated 3 yearly cytology. At 94 CHF HPV based testing was more expensive but cost effective at an ICER converted into CHF 2015 = 6'862 CHF/LYG (compared to 3 yearly cytology with HPV triage)
Assumed cost for cytology in 2015 CHF	35 CHF for normal test, 52 CHF if second reading is necessary
Assumed cost for HPV testing in 2015 CHF	56 CHF in the base case, varied from 32 to 92 CHF

[14] Strategies are shown in order of their effectiveness. ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study.

[15] Strategies are shown in order of their effectiveness. ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study.

Study	Summary[16]	
[76] **Accetta, 2010, Italy**	**With a price for the cytology test of 57 CHF and for the HPV test of 63 CHF, 5 yearly HPV testing with cytology triage had an ICER of 8'990 CHF /QALY while 3 yearly HPV testing with cytology triage was above an acceptable cost effectiveness threshold with an ICER of almost 140'000 CHF/QALY.** **The study had a sensitivity of the HPV assay for HPV presence of only 96% potentially favoring cytology based screening.**	
Deduction of costs and ICERs into CHF by adaption to purchasing power parities and inflation to 2015	Strategies	ICER CHF/QALY
	• Pap test only 5y	Baseline
	• Pap with HPV triage 3y	dominated
	• Pap test only 3y	dominated
	• HPV only 5y	dominated
	• HPV with Pap triage 5y	8'990
	• HPV only 3y	dominated
	• HPV with Pap triage 3y	138'413
Assumed cost for cytology in 2015 CHF	57 CHF	
Assumed cost for HPV testing in 2015 CHF	63 CHF	

[16] Strategies are shown in order of their effectiveness. ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study.

Study	Summary[17]
[35] **Goldhaber-Fieber, 2008, USA**	**At a cost for cytology testing of 55 CHF and of HPV testing of 100 CHF cytology based testing was dominated.** **Interestingly all strategies that started testing below 25 years had ICERs of more than 100'000 CHF/QALY.** **Strategies starting testing at 25 years and older had ICERs below 100'000 CHF/QALY.** **Switching from cytology to HPV testing with cytology triage at 30 years was always clinically more effective but more expensive than switching at 35 years.** **At a switch age of 30 years 5 yearly HPV testing had an ICER of 52'634 CHF/QALY and 3 yearly HPV testing of 96'192 CHF/QALY**
Deduction of costs and ICERs into CHF by adaption to purchasing power parities and inflation to 2015	Strategies Start age with cytology, switch age, strategy after switch ("cyt" for cytology with HPV triage or "HPV" for HPV with cytology triage), frequency in years — ICER CHF/QALY 1.no screening 2.25, none, cyt, 5y — 12'705 3.25, 35, HPV, 5y — 21'779 4.Any, none, cyt, 3y — dominated 5.25, 30, HPV, 5y — 52'634 6.25, 35, HPV, 3y — 67'153 7.25, 30, HPV, 3y — 96'192 8.21, 30, HPV, 3y — 141'566 9.21, 30, HPV, 2y — 221'424
Assumed cost for cytology in 2015 CHF	55 CHF
Assumed cost for HPV testing in 2015 CHF	100 CHF

[17] Strategies are shown in order of their effectiveness. ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study.

Study	Summary[18]	
[32] **Burger, 2012, Norway**	**With a price of 50 CHF for cytology testing and 62 CHF for HPV testing, cytology based testing was dominated. Three yearly HPV testing (6 month follow up time of HPV+/cyt- women) had an ICER of more than 100'000 CHF/LYG. Four yearly HPV testing with 6 months follow up time had an ICER of 97'523 CHF/LYG. With 12 months follow up the ICER went down to 75'630 CHF/LYG. Five yearly HPV testing with 12 months follow up had an ICER of 56'723 CHF/LYG and 6 yearly HPV testing was less effective than 3 yearly cytology with an ICER of 28'859 CHF/LYG**	
Deduction of costs and ICERs into CHF by adaption to purchasing power parities and inflation to 2015	Primary screening test, post-switch (at 31 years) no screening HPV with cotesting triage 6y, 12m time to rescreen cytology 3y HPV with cotesting triage 5y, 12m time to rescreen HPV with cotesting triage 4y, 12m time to rescreen HPV with cotesting triage 4y, 6m time to rescreen HPV with cotesting triage 3y, 6m time to rescreen HPV with cotesting triage 3y, 6m time to rescreen, colposcopy after 1 repeated HPV+/cyt-	ICER (CHF 2015/LYG) — 28'859 Dominated 56'723 75'630 97'523 143'299 510'504
Assumed cost for cytology in 2015 CHF	50 CHF 2015	
Assumed cost for HPV testing in 2015 CHF	62 CHF 2015	

[18] Strategies are shown in order of their effectiveness. ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study.

Study	Summary[19]	
[29] MSAC, 2014, Australia	**Under the assumptions of the Australian model and with cytology test prices of 54 CHF and HPV test prices of 64 CHF, cytology with HPV triage was dominated and 5 yearly HPV testing with cytology triage had an ICER of 29'687 CHF/LYG.** **A screening strategy with 5 yearly HPV16/18 genotyping as primary screening test had an ICER of 89'961 CHF/LYG.**	
Deduction of costs and ICERs into CHF by adaption to purchasing power parities and inflation to 2015	Strategies 1.Current practice Cytology 2y 2. Cytology only IARC intervals 3.Pap +HPV triage IARC 4.LBC + HPV triage IARC 5.HPV + cyt triage 5y 6. HPV16/18 genotyping 5y 7. Cotesting 5y	ICER CHF/LYG dominated baseline dominated dominated 29687 89961 dominated
Assumed cost for cytology in 2015 CHF	54 CHF for Pap, 64 CHF (manually read) or 69 CHF (automatically read) if LBC was the primary screening test	
Assumed cost for HPV testing in 2015 CHF	64 CHF Australian$ for primary HPV testing and 95 if HPV was used as a triage test 96 CHF for cotesting with LBC	

[19] Strategies are shown in order of their effectiveness. ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study.

Study	Summary[20]		
[33] Vijayaraghavan, 2010, Canada	**With the data available for this model and with cytology cost of 21 CHF and HPV costs of 33 CHF 3 yearly cytology with HPV triage had an ICER of 12'783 CHF/QALY and 3 yearly HPV with cytology triage had an ICER of 16'378 CHF. This strategy was dominated by 3 yearly HPV only with direct referral to colposcopy after a positive HPV result with an ICER of 15'180 CHF/QALY. This strategy involves higher colposcopy rates, the burden of which may be only partially reflected in the QALYs as only CIN and Cancer stages had disutilities assigned.**		
Deduction of costs and ICERs into CHF by adaption to purchasing power parities and inflation to 2015		**Screening Strategy***	**ICER CHF/QALY**
		No screening	baseline
		Cytology only 3y	dominated
		Cytology+HPV triage 3y	12'783
		Cytology only 1y	dominated
		HPV+cytology triage 3y	16'378
		Co-screening 3 y	dominated
		Cytology+HPV triage 1y	dominated
		HPV only 3y	15'180
Assumed cost for cytology in 2015 CHF	21 CHF		
Assumed cost for HPV testing in 2015 CHF	33 CHF		

[20] Strategies are shown in order of their effectiveness. ICERs were always calculated against the next less effective strategy on the cost effectiveness frontier of the same study.

21 Kritische Würdigung / Methodenkritik

21.1 Persönliches Fazit

Die Arbeit an diesem Thema hat mir viel Freude gemacht hat. Nach vielen Jahren im Berufsleben, in dem ich viel mit operativen und strategischen Managementaufgaben betraut war, war es eine grosse Befriedigung wieder einmal tief in eine Forschungsarbeit eintauchen zu können.

Ohne Erfahrung mit systematischen Reviews war mir allerdings vor Beginn der Arbeit der Umfang derselben nicht klar. Die Materialfülle und Komplexität der Fragestellungen war enorm.
Während ich erwartet hatte, dass ein Review von Systematischen Reviews und Metaanalysen die geeigneten Kennzahlen zu Benefits und Harms des Screenings und das Vorgehen für den Vergleich verschiedener Screeningstrategien bereits einfach verdaubar beinhalten würden, musste ich lernen, dass dies nicht der Fall war. Besonders die Metaanalysen zielten auf verschiedene, zum Teil überschneidende, aber nicht immer direkt vergleichbare Subaspekte des Themas ab. Daten aus denselben klinischen Studien wurden mehrfach etwas unterschiedlich zusammengefasst, z.T. nach Altersgruppen getrennt, z.T. unter Ein- oder Ausschluss einzelner Studien. Um die Aussagen zu den verschiedenen klinischen Studien nachvollziehen und einordnen zu können, musste ich schliesslich zusätzlich in die Primärliteratur einsteigen und die wichtigsten Publikationen zu den klinischen Studien selbst lesen. Ein alternativer Ansatz für diese Masterarbeit wäre daher gewesen, gleich einen systematischen Review der Primärliteratur zu machen. Obwohl eine Einarbeitung in diese notwendig war, um die Sekundärliteratur zu verstehen, komme ich zum Schluss, dass ein systematischer Review der gesamten Primärliteratur trotzdem wesentlich zu aufwändig gewesen wäre, und dass ein Review der bestehenden systematischen Reviews und Metaanalysen die bessere Methodenwahl war, um im Rahmen einer Masterthesis zu Antworten zu kommen.

Mit fortschreitender Arbeit hat mich die Evidenz zum Thema HPV basiertes Screening zunehmend überzeugt. Sollten die Lesenden dieser Arbeit nicht zu denselben Schlüssen wie ich kommen, so stellt diese Arbeit hoffentlich trotzdem allen Interessierten am Thema einen reichen Datenschatz zur Verfügung, der als Nachschlagewerk dienen kann und als Einstieg in die verschiedenen HTAs und gesundheitsökonomischen Studien für weitere Nachforschungen.

Bei der gesundheitsökonomischen Evidenz stellt diese Arbeit meines Wissens aktuell die umfangreichste Sammlung von gesundheitsökonomischen Daten zum Thema dar.
In diesem Zusammenhang betrachte ich den Appendix 4: “Research question 1a-c – Excerpt of answers from HTAs and Health Economic Studies” als wichtiges Kernstück der Arbeit. Auf wenigen Seiten ist hier eine Übersicht über alle aktuellen gesundheitsökonomischen Studien mit den wichtigsten kosteneffektiven modellierten Screening Strategien zusammengefasst. Ersichtlich sind die wichtigsten Eckdaten aller Studien, die Effektivitätsmessergebnisse sowie die ICERs.

21.2 Methodische Limitationen und nächste Schritte

Ein 4-Augenprinzip wäre für alle Schritte dieses systematischen Reviews ideal gewesen. Bei der Literaturauswahl konnte ich eine zweite Person für ein 4-Augenprinzip gewinnen. Die Übereinstimmung nach der ersten unabhängigen Auswahl der Literatur war hoch und erzielte 100% nach kurzer Diskussion der Gründe für den Ein- oder Ausschluss einzelner Publikationen. Hingegen wurden alle anderen Extraktionen von Informationen und alle Auswertungen aus den Publikationen von mir allein durchgeführt. Bei einer Masterarbeit wäre es mit einem 4-Augenprinzip für alle Aspekte schwieriger gewesen, den Beitrag der verschiedenen Mitwirkenden an der Arbeit voneinander abzugrenzen. In der Durchführung habe ich mich darum bemüht, alle Ausschlüsse von Studien zu beschreiben, sowie Diskrepanzen transparent darzustellen und Interpretationen als solche kenntlich zu machen.

Bei der Transferanalyse habe ich die von Prof. Michael Drummond[21] empfohlenen Fragen gewählt, wie in den Methoden beschrieben. Hier musste ich feststellen, dass nicht alle diese Fragen tatsächlich zu Ein- oder Ausschlusskriterien von Studien führten:

Bei der Frage „Is the viewpoint of the analysis relevant to the Swiss setting“ stellte ich fest, dass grundsätzlich jede eingenommene Perspektive der verschiedenen Studien relevant für das Schweizer Gesundheitssystem sein konnte. Ob nur direkte medizinische Kosten eingeschlossen wurden oder auch indirekte (z.B. Fahrtkosten zu den Screeninguntersuchungen, oder Produktivitätskosten wie die Zeit der Frauen für Screening, Diagnose und Behandlungen), machte in meinen Augen keinen Unterschied für die Relevanz in der Schweiz. Wichtig war hier vor allem die Transparenz über die Art der eingeschlossenen Kosten, da diese die Höhe der ICERs beeinflussen konnten.
Selbst Gesundheitssysteme mit organisiertem Screening wurden von mir als relevante Vergleichssysteme für ein zukünftiges Screening in der Schweiz akzeptiert. Aufgrund der Argumente zu Erfolgsfaktoren für die Umsetzung von HPV basiertem Screening (Forschungsfrage 2) komme ich zum Schluss, dass eine Einführung eines organisierten Screenings auch in der Schweiz sinnvoll wäre. In diesem Fall ist es interessant zu wissen, in welcher Höhe die ICERs von organisierten Screenings liegen. Dieser Punkt ist in der Transferanalyse kenntlich gemacht.

Die möglichen Kosten für den Aufbau eines organisierten Screenings in der Schweiz wurden für diese Masterarbeit nicht eruiert. Dies müsste im Rahmen eines HTAs separat beleuchtet werden, damit die Gesamtkosten über eine längere Zeit inclusive nötiger Investitionen in der Aufbauphase transparent gemacht würden.

Während es bereits einige systematische Reviews zur klinischen Effektivität von HPV basiertem Screening gibt, ist ein vertiefter Review der gesundheitsökonomischen Evidenz mit einer Transferanalyse auf das Schweizer Gesundheitssystem neu.
Aus diesem Grund und angesichts der Materialfülle habe ich mich bei der systematischen Anwendung von Checklisten zur Bewertung der Literatur auf die gesundheitsökonomischen Studien beschränkt.

[21] Prof. Dr. Michael Drummond ist Professor der Gesundheitsökonomie an der Universität von York, UK,
Author des Buches “Methods for the economic evaluation of health care programmes” und hat in verschiedenen Funktioinen massgeblich zur Entwicklung von Methoden für die Evaluation von Gesundheitsleistungen beigetragen.

In der ursprünglichen Projektskizze war der Einsatz der Prisma Checkliste vorgesehen. Nachdem ich mich etwas zum Thema Transferanalysen eingelesen hatte [57], erschien mir jedoch eine Checkliste, die spezifisch für gesundheitsökonomischen Studien und Transferanalysen erstellt wurde, besser geeignet. Aus diesem Grunde habe ich bei den gesundheitsökonomischen Studien die EURONHEED Checkliste angewandt.
Diese Checkliste erlaubte nicht nur die Ermittlung eines Qualitätsdatenscores, sondern erleichterte auch die systematische Extraktion von Daten, die ich für die Studienbeschreibung brauchte (Populationen, Interventionen und Vergleichsstrategien, Diskontierungsraten, Währungen und Kostenjahre etc.).
Hingegen habe ich auf die Anwendung einer Checkliste bei den systematischen Reviews und Metaanalysen verzichtet. Stattdessen wurde ein informeller Check durchgeführt, der sicherstellte, dass die eingeschlossenen Publikationen grundlegende Qualitätsanforderungen erfüllten, wie in den Limitationen dieser Arbeit beschrieben.

Bei der Transferanalyse war es methodisch besonders herausfordernd, die Referenzdaten für das Schweizer Gesundheitssystem zu ermitteln.

In der Analyse habe ich mich für die aktuelle Praxis des Screenings in der Schweiz vollständig auf die Empfehlungen der Schweizerischen Gesellschaft für Gynäkologie und Geburtshilfe abgestützt. Tatsächlich ist es wahrscheinlich, dass diese Empfehlungen in der Praxis nicht 1:1 umgesetzt werden. Die Ergebnisse der Umfrage des BAG von 2014 zeigen zumindest auf, dass viele Ärzte wesentlich öfter zum Screening einladen als empfohlen [96]. Hingegen scheinen andere Aspekte der Empfehlungen wie z.B. der Einsatz von HPV Tests in der Abklärung pathologischer Befunde im Pap-Test gut akzeptiert zu sein. Gemäss einer Umfrage unter Schweizer Gynäkologen von Altermatt sehen von 283 teilnehmenden Gynäkologen 92% eine Bedeutung des HPV-Tests in der Abklärung pathologischer Befunde im Pap-Test [98].
Interessant wäre es in einem nächsten Schritt, Interviews mit Vertretern der Fachärzte zum Thema zu führen und zu erfahren, wie nah die tatsächliche Praxis an den Empfehlungen ist.

Für die Sensitivität des zytologischen Testens in der Schweiz habe ich keine publizierten Daten gefunden. Es ist jedoch wahrscheinlich, dass diese Frage von Fachpersonen in der Schweiz untersucht wurde, und dass auch die durchführenden pathologischen Labore hierzu Daten erheben. Angaben zur tatsächlichen Sensitivität des zytologischen Screenings sollten in einem nächsten Schritt eruiert werden. Auch hier wäre eine Kontaktaufnahme zu Spezialisten möglicherweise zielführend.

Interessante weitere Aspekte sind sämtliche nötigen Implementierungsschritte, damit HPV basiertes Screening in der Schweiz umgesetzt werden kann. Die Antworten zur Forschungsfrage 2 geben zahlreiche Hinweise, welche Voraussetzungen geschaffen werden sollten, damit eine Umsetzung erfolgreich gelingen kann.

Einige mögliche Forschungsthemen in diesem Zusammenhang sind die folgenden Fragen:

- Wie sollte die Kommunikation zum HPV basierten Screening erfolgen, um Stigmatisierung und Verunsicherung der Frauen zu vermeiden und die bestmögliche Teilnahme am Screening und Folgeuntersuchungen zu gewährleisten?
- Welche Massnahmen müssen getroffen werden, um die grösstmögliche Einhaltung der Screeningempfehlungen auf Seiten der Ärzte zu erzielen?

Wichtigste Voraussetzung für die Einführung von HPV basiertem Screening ist die Durchführung eines Health Technology Assessments in der Schweiz. Dies könnte im Rahmen des HTA-Programm des Bundes zur Re-Evaluation von Leistungen der obligatorischen Krankenpflegeversicherung eingeleitet werden.

Ich würde mich freuen, wenn diese Masterarbeit Input zu diesem HTA leisten könnte.

22 Public Health Relevanz

Public Health beschäftigt sich mit der Erhaltung und Förderung von Gesundheit der Bevölkerung oder von Bevölkerungsgruppen, der Vermeidung von Krankheit und Invalidität, sowie der Versorgung der Bevölkerung mit präventiven, kurativen und rehabilitiven Diensten [110].
Sie ist geprägt durch einen interdisziplinären Forschungs- und Handlungsansatz, der gesundheitswissenschaftliche, sozialwissenschaftliche, wirtschaftliche und politische Aspekte einbezieht.

Diese Arbeit ist stark relevant für die Anliegen von Public Health in der Schweiz, da sie sich mit dem Thema Krebsvorsorge für Gebärmutterhalskrebs beschäftigt. Hier geht es um ein Thema, welches die Vermeidung einer Krankheit in der Bevölkerungsgruppe der Frauen zum Ziel hat.
Diese Arbeit vergleicht die Wirksamkeit und Wirtschaftlichkeit des aktuellen Vorgehens mit dem aktuellen Wissensstand der Forschung, bewertet diesen für die Relevanz in der Schweiz und versucht eine Empfehlung abzugeben, wie diese für das weitere Vorgehen in der Schweiz genutzt werden sollten.
Hierbei werden schwerpunktmässig gesundheitswissenschaftliche Aspekte (Wirksamkeit des Gebärmutterhalskrebsscreenings sowie mögliche daraus resultierende Belastungen), und wirtschaftliche Aspekte (Kosteneffektivität des Screenings), aber auch sozialwissenschaftliche Aspekte (Auswirkungen auf die Lebensqualität der betroffenen Frauen, Sicherstellung der Teilnahme von Frauen aus allen gesellschaftlichen Schichten), sowie politische Aspekte (Umsetzungsschritte bei einer möglichen Umstellung des Screenings) beleuchtet.

Das Thema ist aktuell. Im Moment werden in einer zunehmenden Anzahl Ländern Änderungen im Gebärmutterhalskrebsscreening umgesetzt oder empfohlen (z.B. in den Niederlanden, Australien, Belgien, UK, USA). In der Schweiz ist die Einführung eines organisierten Screeningprogramms für Gebärmutterhalskrebs im nationalen Krebsprogramm vorgesehen [61], und eine mögliche Umstellung auf HPV-basiertes Screening in der Schweiz wird diskutiert [1].

Das Thema ist wichtig: Das aktuelle Screening für Gebärmutterhalskrebs in der Schweiz stellt möglicherweise nicht die klinisch wirksamste Methode dar, und ist gleichzeitig möglicherweise in seiner Durchführung teurer als nötig.

Berechnungen des Bundesamts für Gesundheit (BAG) von 2006 zeigten, dass zu diesem Zeitpunkt in der Schweiz jährlich eine Million Pap-Abstriche gemacht wurden, mit denen 70% der Zielgruppe gescreent wurden. Die Hälfte der Abstriche wäre jedoch ausreichend gewesen, um 100% der Zielgruppe zu screenen. Dies ist ein klares Signal, dass einige Frauen zu oft getestet werden, während andere Frauen nie oder zu selten getestet werden. [1] In einer Umfrage des BAG von 2014 stellte sich heraus, dass trotz der Empfehlungen der Fachgesellschaft für Gynäkologie von 2012 für ein dreijährliches Screeningintervall Ärztinnen und Ärzte den Pap-Test bei 78 Prozent der 18- bis 24jährigen Frauen jedes Jahr durchführen, und bei zwei Dritteln der 25- bis 49-jährigen ebenfalls [96]. Zu häufiges Screening erhöht die Kosten, ohne einen Mehrwert für den Schutz vor Krebs zu bringen. Im

Gegenteil erhöht sich dadurch sogar das Risiko von falsch positiven Resultaten und unnötigen Folgeuntersuchungen oder Überbehandlungen [67].
Andere Frauen werden hingegen zu selten getestet. Gemäss der Gesundheitsbefragung von 2007 gaben 79.6% der Frauen (im Alter von mehr als 20 Jahren) an mindestens einmal in ihrem Leben eine Krebsvorsorgeuntersuchung für Gebärmutterhalskrebs gemacht zu haben. Hieraus kann man im Umkehrschluss schliessen, dass 20% der Frauen nie in ihrem Leben gescreent worden sind. Für ausländische Frauen in der Schweiz sowie Frauen, die nur die obligatorische Schule besucht, haben ist dieser Anteil sogar noch höher (ca. 30%)
Eine Unterrepräsentation von Personen mit niedrigem sozioökonomischen Status und die mangelhafte Befolgung von Behandlungsempfehlungen sind typische Merkmale von opportunistischen Screeningmodellen [30].

Hauptaugenmerk dieser Arbeit ist die Technologie der Krebsvorsorge in der Schweiz: das zytologiebasierte Screening mittels Pap-test und Dünnschichtzytologie. Da für die Entwicklung von Gebärmutterhalskrebs eine Infektion mit sogenannten hrHPV Viren die Voraussetzung ist, stellt sich die Frage, ob ein HPV-test nicht besser für ein Screening geeignet wäre. Studien zeigten, dass zytologische Tests gegenüber einem HPV Test eine bis zu 40% niedrigere Sensitivität besitzen, um Frauen zu identifizieren, welche bereits eine Krebsvorstufe entwickelt haben [28]. So hatten in einer US Studie 32% aller Frauen mit invasivem Gebärmutterhalskrebs in den 3 Jahren zuvor ein negatives Ergebnis im Pap-test [23]. Eine Umstellung auf HPV basiertes Screening könnte den daran teilnehmenden Frauen daher eine wesentlich höhere Sicherheit geben, dass keine Krebsvorstufen übersehen wurden, und sie durch das Screening tatsächlich vor Gebärmutterhalskrebs geschützt sind.

Gemäss den Vorgaben des Bundesgesetz über die Krankenversicherung (KVG) müssen die Leistungen, die von der obligatorischen Krankenversicherung vergütet werden, wirksam, zweckmässig und wirtschaftlich sein. Sie müssen periodisch überprüft werden, ob sie diese Merkmale (noch) erfüllen.

Zu diesem Zweck versucht diese Arbeit Fragen zur Wirksamkeit (klinische Effektivität bei möglichst niedrigster Belastung für die betroffenen Frauen) sowie die Wirtschaftlichkeit des aktuellen Screenings mit zytologischen Tests gegenüber einem möglichen Screening mit HPV Tests zu beantworten. Die gewählte Methode war die eines systematischen Reviews klinischer systematischer Reviews und Metaanalysen sowie von HTAs und gesundheitsökonomischen Studien. Es wurde ausserdem versucht zu beurteilen, in wieweit sich die Befunde aus anderen Ländern auf die aktuelle Situation in der Schweiz übertragen lassen.

Die Ergebnisse dieser Arbeit zeigen, dass die Evidenz für die klinische Wirksamkeit eines HPV basierten Screenings gut genug ist, um die ausreichende Wirksamkeit des aktuellen Screenings in der Schweiz in Frage zu stellen. In grosser Übereinstimmung kommen Studien aus verschiedenen europäischen Ländern, den USA, Canada und Australien ausserdem zum Schluss, dass HPV basiertes Screening auch wirtschaftlich ist. Im Vergleich mit 3-jährigem zytologischem Screening zeigten HPV basierte Screeningstrategien häufig sogar eine bessere klinische Wirksamkeit bei niedrigeren Kosten. Auch aus gesundheitsökonomischen Gründen ist das HPV basierte Screening daher interessant.

Für die Implementierung wurden in dieser Arbeit einige wichtige Aspekte genannt, die zum Erfolg eines HPV basierten Screenings beitragen. Allen anderen voran, ist die Sicherstellung der Einhaltung der Screeningempfehlungen identifiziert worden. Hierbei ist die Einführung eines organisierten Screenings die am häufigsten genannte Empfehlung, jedoch möglicherweise nicht die einzig denkbare Lösung. Bis zur Umsetzung der nötigen Massnahmen kann allenfalls die Zweckmässigkeit des HPV basierten Screenings in Frage gestellt werden.

Es sollte jedoch in der Diskussion nicht vergessen werden, dass auch das aktuelle Screening mit zytologischen Tests Schwachstellen hat. Auch eine zu häufige Durchführung der zytologischen Tests kann zu falsch positiven Resultaten und zur unnötigen Entdeckung von regressiven präkanzerösen Läsionen führen. Die Qualität von zytologischen Tests ist ausserdem stärker von den durchführenden Personen abhängig als die Qualität von HPV Tests, die mit Hilfe von automatisierten Laboranalysesystemen durchgeführt werden.
Die Einführung eines organisierten Screenings sollte aufgrund der besseren systematischen Qualitätskontrolle und des möglichen besseren Einbezugs der Frauen aus allen Bevölkerungsschichten deshalb auch unabhängig von der Einführung einer neuen Technologie diskutiert werden.

Aus Public Health Sicht ist klar, dass die wissenschaftliche Evidenz allein für eine erfolgreiche Umsetzung einer gesundheitspolitische Massnahme nicht ausreicht.

Sehr wichtig für die erfolgreiche Umsetzung eines neuen Screeningprogramms ist z.B. die Einbindung der wichtigsten Interessen- und Anspruchsgruppen. Diese sind in diesem Zusammenhang die Kantone, die Ärzte, die Frauen, die Krankenkassen, sowie die Pathologen und Diagnostiklabors [98]. Hierbei spielen sowohl monetäre Interessen als auch persönliche und politische Einstellungen eine Rolle.

Monetäre Interessen könnten die Kantone haben, die im Falle der Einführung eines organisierten Screenings Infrastruktur aufbauen müssten. Die Gynäkologen könnten finanzielle Einbussen erleiden, wenn längere Intervalle für das Screening umgesetzt werden. Die Krankenkassen könnten ein monetäres Interesse am neuen Screening haben, wenn es kostengünstiger als das aktuelle ist. Die Frauen könnten profitieren, wenn sie weniger häufig zum Screening gehen müssten und weniger Tests im Rahmen ihrer Krankenkassenfranchise selbst zahlen müssten. Die Pathologen würden mit einem HPV basierten Screening weniger zytologische Tests durchführen, die Diagnostiklabors hingegen mehr.

Die Einstellungen der Gynäkologen zum aktuellen Screening scheint positiv zu sein [98]. Eine Änderung zum Status Quo kann auch als Bevormundung durch den Gesetzgeber angesehen werden.
Auch die Frauen sind an das aktuelle Screening gewöhnt. Die Einführung einer neuen Technologie und längerer Screeningintervalle kann verunsichern [98]. Die Kommunikation der Gründe und der Evidenz für das neue Vorgehen müssen daher gut vorbereitet und begleitet werden. In den USA haben Frauen die Wahl zwischen 3-jährigem zytologischen Screening und 5-jährlichem Cotesting. Auch in Deutschland ist vorgesehen im Rahmen der Einführung eines organisierten Screenings den Frauen in den ersten Jahren der Einführung

die Wahl zwischen jährlichem zytologischem und 5 jährlichem HPV basierten Screening zu geben. Anschliessend ist eine vergleichende Evaluation beider Strategien vorgesehen [111]. Diese Beispiele zeigen, dass die Umsetzung einer neuen Screeningstrategie den Präferenzen der Betroffenen Rechnung tragen kann.

Die Umsetzung eines neuen Screeningmodells für die Vorsorge des Gebärmutterhalskrebs beschäftigt sich mit der Gesundheitsvorsorge der Bevölkerungsgruppe der Frauen. Sie berührt mit all seinen Facetten gesundheitswissenschaftliche, sozialwissenschaftliche, wirtschaftliche und politische Aspekte und ist ein daher Public Health Thema von hoher aktueller Relevanz.

23 Selbständigkeitserklärung

Eine zweite Person (Dr. Jacqueline Sayers) unterstützte die Auswahl der Literatur im Sinne eines 4-Augenprinzips, damit der Einschluss und Ausschluss von Studien auf objektiven Kriterien beruht. Frau Sayers sah die Arbeit zusätzlich auf korrektes Englisch durch.

Hiermit erkläre ich, dass ich die gesamte Arbeit selbständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt habe. Alle Stellen der Arbeit, die wörtlich oder sinngemäss aus Quellen entnommen wurden, habe ich als solche kenntlich gemacht.

01 Juli 2016, Martina Hahn

24 Curriculum Vitae

Personal Data

Name	Dr. Martina Hahn
Date of Birth	November 20, 1964
Marital Status	married, one daughter
Citizenship	German
Private Address	Weidstrasse 14 CH-6300 Zug Phone +41 76 460 2555 e-mail: martina.l.hahn@gmail.com
Business Address	Head BGE Quality Roche Diagnostics International Ltd. Forrenstrasse 2 CH-6343 Rotkreuz Phone +41 41-799 2773 Mobile: +41 79-252 6970 e-mail: martina.hahn@roche.com

Education

Year	Location	Graduation
Since 2012	University of Zurich Student of Public Health	
1997-1998	SAQ, Olten	Quality System Manager
1990-1994	Dissertation University of Heidelberg, Roche Basel	PhD „Doktor der Naturwissenschaften“
1983-1989	Studies in Biology University of Heidelberg, Germany	Biologist

Professional career

Year	Place	Function
Since Feb 2016	Roche Diagnostics International Ltd. Rotkreuz	Head BGE Quality
Jan 2012 - Feb 2016	Roche Diagnostics International Ltd. Rotkreuz	Head of Special Projects in Quality and Compliance
Aug 2000-Jan 2012	Roche Diagnostics Ltd. Rotkreuz	Head Quality Management Rotkreuz and Global Platforms and Support
Aug 98-Jul 2000	Roche Instrument Center AG Rotkreuz	Head Quality Control Immunochemical Diagnostic Instruments
Oct 94-Jul 98	Roche Diagnostics Kaiseraugst	Head Quality Control Immunochemical Assays for Hormones and Tumor Markers
Jan-Sep 1994	Roche Pharma Basel Department Cardiovascular Preclinical Research	Postdoctoral Fellowship
1990-1993	Roche Pharma Basel Department Neurobiology Preclinical Research	PhD Student
1986-1990	University of Heidelberg	Research Assistant

25 Time used for the Thesis

A total time of approximately 800 hours was used for the thesis

Table 16: Time used for the Thesis

Phase		Effort (hours)
0	Project proposal	60
1	Literature search	120
2	Analysis of clinical evidence	160
3	Extraction of answers to research questions from economic studies	80
4	Evaluation of the quality / reliability of answers	80
5	Evaluation of the transferability of answers to the Swiss setting	80
6	Analysis of information on feasibility	40
7	Discuss conclusions for potential policy changes for the Swiss screening setting	40
8	Writing, reviews, revisions	150
	Contact times with Matthias Schwenkglenks	10
	Sum	**820**

26 Declaration of Interest

The author is an employee of Roche Diagnostics. In addition she owns Roche shares.
At Roche Diagnostics she works for the function of Global Quality and Regulatory Affairs. This function is responsible that quality and compliance is effectively maintained through efficient and effective processes and worldwide regulatory requirements are met, in order to provide customers and patients with reliable high-quality products and services.
This function is organizationally independent of development, production, sales and marketing functions and the author is not involved in the development, production nor sales or marketing of the HPV assay. This thesis is done in her free time.

Dr. Jacqueline Sayers is a former employee of Roche Diagnostics. At her time at Roche Diagnostics she did not have any relation to any function related to HPV testing. There are no potential conflicting interests from her side.

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